FORMULATION AND EVALUATION OF FLOATING BILAYER TABLET OF METFORMIN HYDROCHLORIDE AND GLIMEPIRIDE

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By

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TIRUCHIRAPPALLI - 620 021

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Ms. N.Pavala Rani, M.Pharm., Ph.D.,
Lecturer,
Department of Pharmaceutics,
Periyar College of Pharmaceutical Sciences for Girls,
Tiruchirappalli – 620 021.

CERTIFICATE

This is to Certify that the dissertation entitled **"FORMULATION AND EVALUATION OF FLOATING BILAYER TABLET OF METFORMIN HYDROCHLORIDE AND GLIMEPIRIDE"** submitted by **Ms. P. RAJALAKSHMI [Register Number: 26102206**] for the award of the degree of **"MASTER OF PHARMACY"** is a bonafide research work done by her in the Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirappalli under my guidance and direct supervision.

Place : Tiruchirappalli

Date :

(MS.N.PAVALA RANI)

Forwarded

Prof. Dr. R. Senthamarai, M.Pharm., Ph.D.,
Principal,
Periyar College of Pharmaceutical Sciences for Girls,
Tiruchirappalli – 620 021.

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This dissertation is submitted for acceptance as project for partial fulfillment of the degree of **"MASTER OF PHARMACY"** in **Pharmaceutics**, of The Tamilnadu Dr. M.G.R Medical University, during May 2012.

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Date: **(Dr. R. SENTHAMARAI)**

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ABBREVIATIONS

ABBREVATIONS	EXPANSION
HPMS	Hydrophilic Polymer Matrix system
US FDA	United State Food And Drug Administration
HPMC	Hydroxy Propyl Methyl Cellulose
GRDDS	Gastro Retentive Drug Delivery System
DF	Dosage Form
CR-DFS	Controlled Release Dosage Form
HBS	Hydrodynamically Balanced System
GI	Gastric intestine
GRT	Gastric Residence Time
MMC	Migrating Myoelectric Complex
FDDS	Floating Drug Delivery System
IDF	International Diabetes Federation
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non-Insulin Dependent Diabetes Mellitus
OHA	Oral Hypoglycemic agents
DM	Diabetes Mellitus
HCl	Hydrochloride
SR	Sustained Release
IR	Immediate Release

1.1 **Sustained Drug Delivery system** [1,2]

There has been 60 years of research and development experience in the sustained drug release area since the patent, and a number of strategies have been developed to prolong drug level in the body. With many drugs, the basic goal of therapy is to achieve a steady-state blood or tissue level that therapeutically effective and non-toxic for an extended period of time.

In the recent past, controlled release concept and technology have received increasing attention in the face of growing awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional methods. Thus drugs applied in the form of tablets, capsules, injectables and ointments etc., usually produce wide range of fluctuations in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor as well such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems or therapeutic systems[3]. A dosage form that one or more drugs continuously in a pred pattern for a fixed period of time, either systematically or to a specified target organ is a controlled drug delivery system. The event of drug delivery system brings rate controlled delivery with fewer side effects, increased efficacy and constant delivery. The primary objective of controlled drug delivery systems is to ensure safety of drugs as well as patient compliance.

The goal of any drug delivery systems is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. Two aspects are most important to drug delivery, namely spatial placement and temporal delivery of a drug[4]. Spatial placement related to targeting drug to a specific organ or tissue. While temporal delivery refers to controlling the rate of drug delivery to the target tissue.

1.1.2Requirements for sustained drug release[4]

Design of sustained release products is normally a very difficult task because of interplay of the physical-chemical-biological properties of the drug, the patient disease state and technological limitations in fabrication of the final dosage form. Depending upon the drug, disease state, route of administration, but before a final decision is made to proceed with the dosage form; all these factors must be considered.

1.1.3Advantages of Sustained Release Dosage Form[5]

i. Frequency of drug administration is reduced.

ii. The Patient compliance can be improved, and drug administration can be made more convenient.

iii. blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced, because a more even blood level is maintained.

iv. Implicit in the design of sustained release forms, is that the amount of drug administered can be reduced, thus maximizing availability with a minimum dose.

v. The safety margin of high-potency drugs can be increased, and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

1.1.4 Disadvantages

i. Administration of sustained release medication does not permit the prompt termination of therapy.

ii. The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form regimen.

iii. Sustained release forms are designed for the normal basis of average drug biologic half-lives. Consequently, disease states that alter drug disposition, significant patient variation, so forth are not accommodated.

iv. Economically more costly processes and equipment are involved in manufacturing many sustained release forms.

1.2. Hydrophilic Polymer Matrix System (HPMS)

Hydrophilic Polymer Matrix System (HPMS) are widely used in oral controlled drug delivery because they make it easier to a desirable drug-release profile, as they are cost effective and have abroad US FDA acceptance. It consists of hydrophilic polymer, drug and other excipients distributed throughout the matrix[6]. This dynamic system is dependent on polymer wetting, hydration and dissolution for controlled release of drug. At the same time, other soluble excipients (or) drug substance will also wet, dissolve and diffuse out of the matrix, whereas insoluble excipients (or) drug substances will be held in place until the surrounding polymer, excipients (or) drug complex erodes (or) dissolves away.

Matrix controlled release tablet are relatively simple system that are more forgiving of variations in ingredients, production methods and end-use conditions when compared to coated controlled release tablets of other systems. This results in more uniform release profiles with a high resistance to drug dumping. Hydrophilic matrix systems are relatively easy to formulate with existing conventional equipments and processing method[5]. One goal of this study was to develop uncoated HPMC matrix tablet by wet granulation process, evaluating the relationship and influence of excipients.

1.2.1 Advantages of hydrophilic matrix system

- Generally regarded as a safe excipient
- Simple concept
- Erodable – reducing ghost matrices
- Easy to manufacture by
    - Direct compression
    - Wet granulation
    - Roller compaction
- Possible to obtain different release

1.2.2 Disadvantages

- Need optimal rate controlling polymers
- Scale of problems
- Release of drug depends upon penetration of water and diffusion of drugs through hydrated matrix
- If outer matrix layer erodes, complication in drug release profile takes place.

These matrix tablets are resistant to dose dumping due to simple nature of formulation by hydrophilic colloid matrices are being robust they are unaffected by variation in ingredients. An important factor for modified release is the ability of hydrophilic polymers to readily hydrate and form a gel.

Hydroxy Propyl Methyl Cellulose (HPMC), which is commonly used in HPMS. It is a mixed alkyl hydroxyl alkyl cellulose other containing methoxy & hydroxyl propyl groups. The hydration rate of HPMC increases with increase in hydroxyl propyl content. The solubility of HPMC is pH independent. It is non-ionic

and tolerant of most formulation variables and under very controlled conditions yield consistent properties of reproducible performance.

Evidence suggests that the chemistry of HPMC encourages a strong tight gel formation compared to other . As a result, drug release rates have been sustained longer with HPMC than with equivalent levels of hydroxyl methylcellulose, ethyl cellulose (or) carboxyl methylcellulose. In addition, it was found that kinetics of initial hydration of cellulose ether is quite fast and relatively independent of substitution. Kinetics of gel growth is very similar for all substitution types of HPMC, observed apparent differences in swelling behavior are attributed to differential expansion of the glossy core[7].

Polymer chemistry plays a significant role since gel strength is controlled by polymer viscosity of concentration. Because HPMC is available in a wide range of molecular weights, effective control of gel viscosity is easily provided. It is the polymer most widely used in the formulation of solid, liquid semisolid and even controlled release dosage forms as gel forming agent. Water penetration, polymer swelling, drug dissolution and diffusion, matrix erosion from these dosage forms are controlled by the hydration of HPMC, which forms a gel barrier through which drug diffuses.

1.2.3 Mechanism of drug release from hydrophilic matrix system[8]

On exposure to aqueous fluid, hydrophilic matrices take up water, and polymer starts hydrating to form a gel layer. Drug release is controlled by diffusions barriers / or by surface erosion. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy polymer comes in contact with an aqueous medium, there is an abrupt change from a glassy to a rubbery state which is associated with swelling process with time, water infiltrator deep into the case increasing the thickness by the gel layer. Concomitantly the outer layer

becomes fully hydrated and states dissolving or eroding. When water reaches the center of the system and the concentration of drug fells below the solubility value, the release rate of drug begins to reduce. At the same time, an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release. Drug release kinetic associated with these gel – layer dynamic, range initially from Fickian to annomalous (Non – Fickian) and subsequently from quasi – Constant (near Zero order) to constant.

In general, two major factors control the drug release from swelling controlled matrix system. They include

- The rate of aqueous medium infiltration into the matrix, followed by a Relaxation process (ie.,hydration,gelation,swelling).
- The rate of matrix erosion.

As a result of these simultaneous processes, two front are evident, a swelling front, where the polymer get hydrated, and an eroding front. The distance between these two fronts are called diffusion layer thickness. Diffusion layer thickness depends on the selective rate at which the swelling and eroding fronts move in relation to each other. If the polymer gets slowly, solvent can penetrate deep into the glassy matrix the dissolving the drug; there for gel layer thickness and it stability are council in controlling drug release.

Swelling of HPMC matrix tablet was higher for higher a molecular weight. They attributed this to the large hydrodynamic volume occupied by higher molecular weight chain when hydrated. As the polymer chain becomes more hydrated and the gel becomes more dilute, the disentanglement concentration may be reached that is, the critical polymer concentration below which the polymer chain disentangle and detached from gelled matrix.

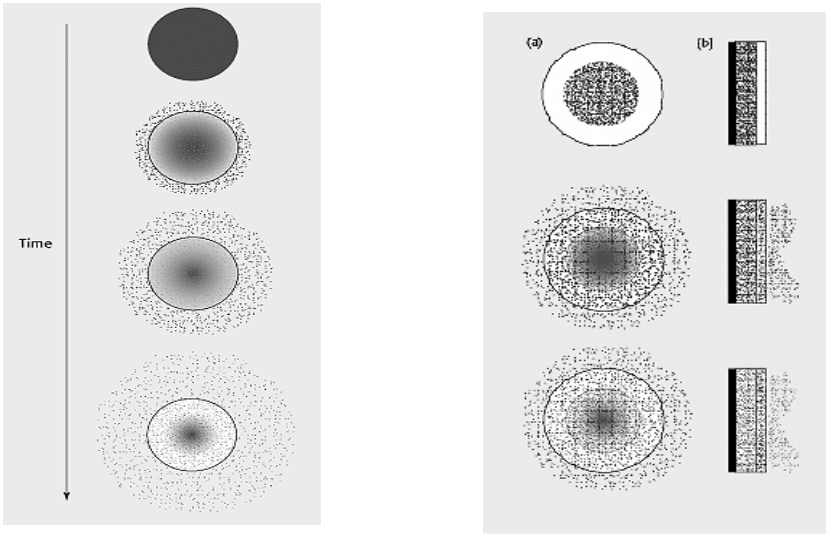


Fig – 1

Mechanism of Drug Release from Hydrophilic Matrix System

The mechanism by which drug release controlled in matrix tablet is dependent on many variables, however the main principle is that the water soluble polymer present throughout the tablet hydrates on the outer tablet surface to form a gel lager. Throughout the life of the ingested tablet, the rate of drug release is deferment by diffusion (if soluble) through the gel and by the rate of tablet erosion (if insoluble).

1.3BILAYER TABLET[9,10]:

A type of multilayered tablet in which instead of single tablet two layers were formulated by which two incompatible drugs can also be combined together in same formulation.

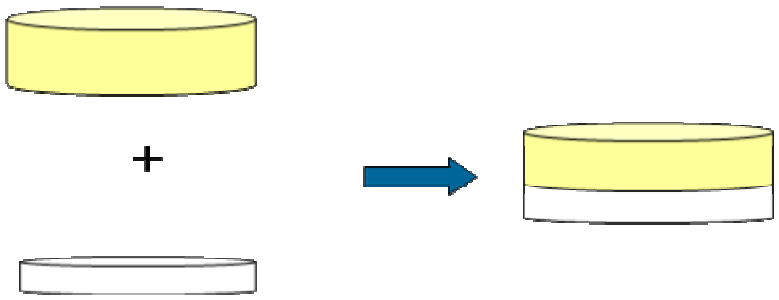


Fig – 2

Bilayer Tabletting

3.2Advantage[11]

- A new platform technology for decreasing the chemical incompatibility.
- Release of one drug as immediate and another drug as sustained.
- Two layers are visible, so unbinded tablets can be easily detected.
- Less coating material is required.

3.3 Rationale for Development of Bilayer Tablet Technology:

- Patient convenience
- Patient Adherence.
- Monotheraphy was prevented & Reduces pill burden
- Combination of incompatabile drugs.
- Ease of manufacture
- Elegance to the product
- Improved product stability.
- Release of both the drugs starts immediately
- Least probability of developing drug resistence used to treat different ailments at the same time in with one pill such as Hypertension, Heart disease, Hyperlipidemia, obesity & Diabetes.
- Incompatability / stability issues can be resolved.

A new platform technology for decreasing the mechanical shear on double compressed products which can lead to decrease in unknown/process related impurities

4.1Introduction of Gastric Retentive Drug Delivery system[12]

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters to their performance. Despite tremendous advancements in drug delivery, the oral route remains the preferred route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance.

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems(GRDDS). The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed[12]. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and

can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine). All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS).

NEED FOR GASTRIC RETENTIVE DRUG DELIVERY SYSTEMS:

To prolong the drug release and to reduce the variable gastric emptying process. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner, So that the drug could be supplied continuously to its absorption sites in the upper gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs[13]. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs.

The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches.

(a) Low density form of the DF that causes buoyancy in gastric fluids.
(b) High density DF that is retained in the bottom of the stomach.
(c) Bioadhesion to stomach mucosa.

(d) Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients.

(e) Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.

The current review deals with the gastro retentive approaches that has recently become leading methodologies in the field of controlled and site specific drug delivery system.

Advantages of floating drug delivery system

1. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
2. The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease[14] e.g. antacids.
3. The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
4. Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline PH of the intestine.
5. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such

circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

6. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
7. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine
8. Certain types of drugs can benefit from using gastro retentive devices. These include:

- Drugs acting locally in the stomach;
- Drugs those are primarily absorbed in the stomach;
- Drugs those are poorly soluble at an alkaline pH;
- Drugs with a narrow window of absorption;
- Drugs absorbed rapidly from the GI tract; and
- Drugs those degrade in the colon.

Disadvantages of floating drug delivery systems

1) There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
2) Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems.
3) Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

Factors affecting the floating drug delivery system

- Nature of meal – feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.
- Frequency of feed – the GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC[15].
- Gender – mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface).
- Age – elderly people, especially those over 70, have a significantly longer GRT.
- Posture – GRT can vary between supine and upright ambulatory states of the patient.
- Concomitant drug administration – anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
- Biological factors – diabetes and Crohn's disease, etc.

Biological aspects of GRDFS:

Role of GI tract: Stomach

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small

surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.

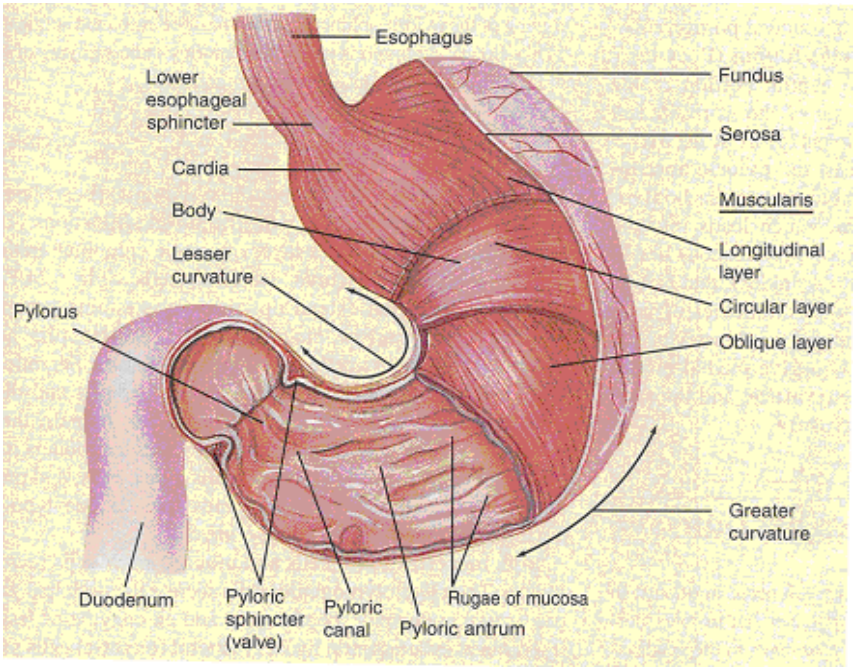


Fig.3

Anatomy of Stomach

The stomach is divided into three anatomical regions. I)Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted of Fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states[16].

The GI tract is always in a state of continuous motility. There are two modes of motility pattern. The digestive mode and interdigestive mode. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as

interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is further divided into four phases.18,19

Phase I	:	Period of no contraction.
Phase II	:	Period of intermittent contraction.
Phase III	:	Period of regular contractions at the maximal frequency that migrate distally.
Phase IV	:	Period of transition between phase III and phase I.

Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the house keeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle.

Approaches to gastric retention[17]

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include –

a) Floating Systems
b) Bio/Muco-adhesive Systems
c) Swelling and Expanding Systems
d) High Density Systems
e) Incorporation of Passage Delaying Food Agents
f) Ion Exchange Resins
g) Osmotic Regulated Systems

Floating Systems:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, noneffervescent and effervescent systems.

Effervescent system:

These are matrix types of systems prepared with the help of swell able polymers such as methyl cellulose and chitosan and various effervescent compounds.eg,sodium bicarbonate ,citric acid and tartaric acid.

They are formulated in such a way that when in contact with the acidic gastric contents,co_2 is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

Non-effervescent system

- These system use a gel forming or swell able cellulose type hydrocolloids and matrix-forming polymers like polyacrylate, polycarbonate, etc.
- The formulation method of this system is thoroughly mixing the drug and the gel forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains the bulk density of < 1.
- The air entrapped within the swollen matrix imparts buoyancy to the dosage forms.

FLOATING BILAYER TABLET

These are also compressed tablet as shown in Fig 3 and containing two layer i.e.,

i. Immediate release layer and

ii. Sustained release layer.

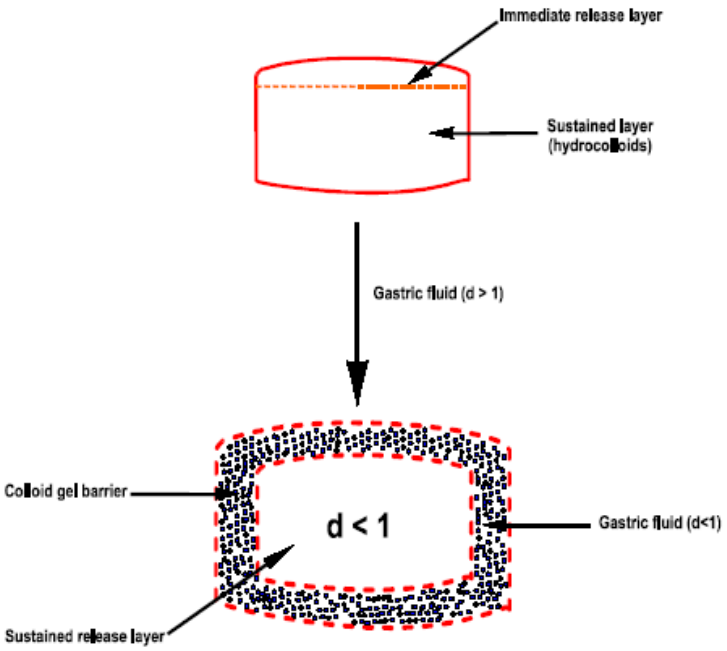


Fig 4

Floating Bilayer Tablet

1.5 DIABETES MELLITUS[18,19]

Diabetes mellitus is a metabolic disorder characterized by high blood sugar (glucose) level or hyperglycemia, glycosuria, hyperlipemia, negative nitrogen balance sometimes ketonemia. The above symptoms results in defect of insulin secretion or action or both. A wide spread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerullar capillaries, retinopathy, neuropathy and peripheral vascular insufficiency. Diabetes mellitus consists of group of disorders involving distinct pathogenic mechanism with hyperglycemia as the common effect. Regardless of the cause, the disease is associated with insulin deficiency, which may be total or partial or relative when viewed in respect of co-existing insulin resistance. Diabetes is a major medical and economical problem. Hence, in order to treat this highly prevalent condition, many pharmaceutical preparations have emerged in the recent past which are termed as Antidiabetic agents.

Diabetes mellitus is the commonest endocrine disorder also now recognized serious global health problem. It affect more than 100 million of the people worldwide.

The INTERNATIONAL DIABETES FEDERATION (IDF) estimates the total number of people in India with diabetes to be around 50.8 million in 2010, rising to 87.0 million by 2030. In more developed societies, the prevalence of Diabetes mellitus has reached about 6% and even more alarmingly, among obese white adolescents 4% had diabetes and 25% had abnormal glucose tolerance. Some 90% of diabetic individuals have Type 2 diabetes mellitus when compared to Type 1 diabetes mellitus[20]. Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the

risk of long-term complications.The lifestyle modification, diet and exercise of moderate intensity are used to improve insulin sensitivity and are recommended as an integral part of treatment of Type 2 diabetes[21]. When the lifestyle modification, diet and exercise fails to maintain the adequate glyceamic control, oral hypoglycemic agents are introduced as a treatment approach.

Diabetes Mellitus can be categorized into several types but the two major types are

- **Type 1 Diabetes Mellitus**

  Also known as Insulin dependent diabetes mellitus (IDDM) or juvenile-onset diabetes.

- **Type 2 Diabetes Mellitus**

  Non-insulin dependent diabetes mellitus (NIDDM) or maturity- onset diabetes.

Type 2 Diabetes would affect about 98% persons above 45 years of age.
Type 2 diabetes is caused by two primary metabolic defects:

Progressive pancreatic β-cell dysfunction and insulin resistance. β-Cell dysfunction superimposed on insulin resistance leads to hyperglycemia and subsequently to type 2 diabetes. Typically, at the time of diabetes diagnosis, nearly 50% of β-cell function has been lost and less than 60% of normal insulin sensitivity is present.

Oral Hypoglycemic Agents (OHAs) can be used either alone or in combination with other OHAs or insulin. The Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes recommends a target hemoglobin A1C concentration of 7.0% or less for all patients with diabetes. Currently, there are five major classes.

Oral Anti Diabetic agents[22]:

Sulphonylureas

– insulin secretagogues that target β –cell dysfunction.

Metformin

– a biguanide that reduces hepatic glucose production and improves insulin sensitivity.

Thiazolidinediones

– insulin sensitizers that lower peripheral insulin resistance

β-glucosidase inhibitors

– intestinal enzyme inhibitors that slow carbohydrate absorption; and

Meglitinides

– rapid but short-acting,

The goal levels of diabetes related parameters during treatment is given in Table No.

Table no: 1

Blood-glucose targets for people with Diabetes

Parameter	Normal	Goal	Action suggested if
Pre-prandial Fasting Glucose	<110 mg/dl	80-120 mg/dl	<80 or >140 mg/dl
postprandial Glucose	<140 mg/dl	<140 mg/dl	>180 mg/dl
Bedtime	<120 mg/dl	100-140 mg/dl	<100 or >160 mg/dl
HbA1c	≤ 6%	< 6.5 %	>8 %

Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications.

Insulin is indicated in the following situations:

1) When diet and oral hypoglycemic drugs fail to control hyperglycemia and achieve therapy targets
2) Diabetes during pregnancy when diet alone is inadequate
3) When oral hypoglycemic drugs are contraindicated
4) During stressful conditions such as infection and surgery.

Combination therapy:

It was always beneficial to switch over the patients on combination therapy, when there is high secondary failure associated with monotherapy and devastating long term consequence of poor glycemic control. Areasonable goal of treatment is to maintain good glycemic control through combination therapy so as to keep HbA1c value below 7% for a particular patient. Initiation of combination drug therapy at low dosages can minimize the side effects associated with high dose therapy of either agent, yield additive clinical benefits, and possibly curtail cost of treatment. For many drugs, 50% of the dosage needed to achieve the maximal therapeutic effect will produce well over 50% of that effect.

Table no: 2

Comparison of Type 1 & type 2 DM[23]

Parameters	Type 1	Type 2
Age of onset	<40 years	>50 years
Classical symptoms	Usually present	Few or none
Duration of symptoms	weeks	Months/years
Body weight	Normal/low	Obese usually
History of weight loss	yes	No
Prone to ketoacidosis	yes	No
Insulin levels	Very low	Low/Normal/High
Insulin resistance	Absent	Present
Rapid death without insulin	yes	No
Presence of autoantibodies	yes	No
Diabetic complications at diagnosis	No	10-20%
Family history of diabetes	No	Yes
Presence of other auto immune disease	Yes	No
Complications	Microvascular, Macrovascular	Microvascular, Macrovascular

[24]**Biswajit Biswal et al., (2011)** were studied on designing floating Bilayer tablet of Trimetazidine Dihydrochloride by dry granulation method. The formulated tablets were evaluated for weight variation, hardness, friability, drug content, floating lag time, total buoyancy time and *in vitro* release studies. He reported that the combination of low viscosity polymer and high viscosity polymer would increase the release rate.

[25]**Rubina Reichal et al., (2011)** were developed the floating tablet of Glimepiride by direct compression technique by using various viscosity grades of HPMC k4M, HPMC K100 and Carbopol 934P to prolong the gastric residence time and to increase the drug bioavailability.

[26]**Gaur et al., (2011)** were designed the floating tablet of Metformin HCl by optimizing gas generating agent to improve the buoyancy time. He found that increasing concentration of sodium bicarbonate results in bursting effect.

[27]**Padmavathy et al., (2011)** were studied on formulating floating tablet of Oflaxacin using HPMC by wet granulation technique. She reported that the drug release rate decreased as the concentration of high viscosity polymer increased.

[28]**Pramod patil et al., (2011)** were fabricated floating tablet of Oflaxacin by wet granulation method. He concluded that HPMC K100 shows decrease in floating lag time & increase the duration of floating time. This is due to high viscosity polymer HPMC K100 maintains the integrity of the tablet for longer duration.

[29]**Sivabalan et al., (2011)** were designed floating Glipizide tablet by direct compression technique. He found that by combining the polymer like HPMC, EC (ethyl cellulose) and MCC (microcrystalline celluose) shows better *in vitro* release than polymers alone.

[30]**Garg shiv kumar et al., (2011)** were studied on Gastroretentive floating tablet of Aceclofenac by using HPMC K4M, HPMC K15M by direct compression method. He found that drug release rate decreased in order of HPMC K grade < HPMC E grade with increasing macromolecular weight, the degree of entanglement of the polymer chain increase. So, the mobility of the macromolecules in the fully swollen system decreased this leads to decreased drug diffusion and decreased drug release with increase in molecular weight.

[31]**Madhu soodan Sharma et al., (2011)** designed the floating tablet of Cefpodoxime proxetil by employing different viscosity grades of HPMC K4M,K15M,K100M at different drug to polymer ratio. He reported that the different viscosity grades in different ratio would effect the drug release.

[32]**Laxmi goswami,et al., (2011)** fabricated Bilayer Floating Tablet of Metformin HCl and Pioglitazone was done by direct compression using polymers like hydroxyl propyl methyl cellulose(HPMC),Carbopol, Polyvinylpyrrolidone to facilitate immediate release of pioglitazone and sustained release of Metformin HCL. The formulated tablets remain buoyant over a period of 12-20 hrs and released more than 80% of drug in study period.

[33]**Dinesh kumar et al., (2010)** formulated the Bilayer tablet of Raniditine by direct compression method. HPMC K100, HPMC K4M, HPMC E-15 were used as gel forming agents and sodium bicarbonate are used as gas generating agent. The formulated tablets were evaluated for weight variation, drug content, floating lag time and duration of floating. The results shows that good floating property and sustained release character.

[34]**Ajay Bagherwal et al., (2010)** studied on formulating Ciprofloxacin HCl floating tablet by dry granulation method. The formulated tablets were characterized for weight variation, hardness, friability, drug content, floating lag time, total buoyancy time and *in vitro* dissolution study. From the release studies it was concluded that increase in polymer concentration decreases the release rate.

[35]**Borkar et al., (2010)** studied the effects on viscosity of polymer in formulating Bilayer gastroretentive floating drug delivery system of Cefpodoxime proxime. From the study it was concluded that the drug release decrease with increase in concentration of polymer. To overcome an initial burst effect, the high viscosity HPMC polymer used. High viscosity polymer give prolonged floating and drug release when compared to low viscosity polymer.

[36]**Mohammed asif et al., (2010)** fabricated on gastroretentive dosage form of Fluvastatin sodium. He concluded that viscosity was the major effect affecting the release and floating property. On increasing the concentration of hydrogel polymer it decreases the release rate.

[37]**Rajashree masareddy et al., (2010)** were designed floating matrix tablet of Riboflavin by direct compression method using HPMC K4M and Carbopol 971P mixture. The studies revealed that combination of low viscosity and high viscosity polymer the was found to better for formulating sustained release.

[38]**Margret chandira et al., (2010)** were formulated gastroretentive drug delivery system of gastro prokinetic drug Itopride HCl employing polymers like HPMC K100M, HPMC K15 & Carbopol934P. she proved that drug release rate was decreased as the viscosity of the polymer increased.

[39]**Barhate et al., (2010)** were optimized floating Bilayer tablet of Famotidine by wet granulation technique. He concluded that drug release rate deponds on the combination of low viscosity and high viscosity.

[40]**Anilkumar shinde et al., (2010)** were studied on formulating floating tablet of Cephalexin using HPMC as rate retarding agent, sodium bicarbonate as gas generating agent. The studies revealed that increase in concentration of polymer the release rate was decreased.

[41]**Dalavi et al., (2009)** fabricated on Gastroretentive drug delivery system of an antiretroviral agent Zidoviduine and evaluated on statistical analysis. His studies confirmed that the formulation which contains high polymer concentration, were able to keep their integrity and show better control on *in vitro* release studies, with a desired slower release rate for a prolonged period of time.

[42]**Selimreza et al., (2009)** designed in formulating theophylline loaded gastroretentive floating tablet by employing HPMC K4M & HPMC K15 and gas generating agent. He reported that increase in amount of floating agent cause the decrease in floating time and high amount of hydrophilic polymers would favoured for formulating Sustained release.

[43]**Swati jagdale et al., (2009)** were studied on formulating the gastroretentive drug delivery system of propranolol HCl various polymers like HPMC KM, HPMC E-15, HPC in various proportions. He found that low viscosity polymers increase the floating lag time but decrease the release rate. The high viscosity polymer HPMC K4M gave good release rate when compared to HPMC E-15.

[44]**Ravikumar et al., (2009)** studied on designing effervescent floating tablet of Famotidine by direct compression technique. His studies confirms that the formulation in combination of different viscosity grades of HPMC polymer shows better release and it is suitable for formulating SR formulations.

[45]**Kshirsagar et al., (2009)** were studied on effect of different viscosity grade HPMC polymers on gasteoretentive drug delivery of Metformin HCl. He reported that viscosity of polymer increases in the formulation the release decreases, which may be due to increased strength of the gel matrix of the HPMC.

[46]**Shailesh et al., (2008)** studied on designing gastric floating matrix tablet by using combination of polymers. He found that HPMC was a suitable polymer for developing floating tablet.

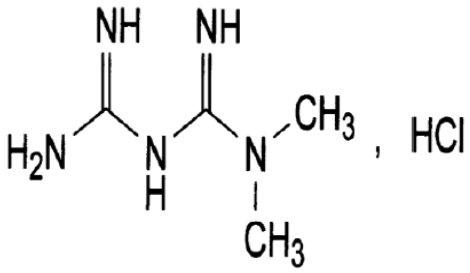
[47]**Patil et al., (2008)** designing floating tablet of Amlodipine besylate by incorporating different grades of polymers. His study reveals that by combining HPMC K100M & HPMCK15M the release rate was prolonged.

[48]**Tanwar et al., (2007)** formulated famotidine floating tablet by using two different grades of Methocel K100 and Methocel K15M. He found that Methocel K100 were found it is suitable for floating technique due to its prolonged action.

3.1 DRUG PROFILE

3.1.1 Metformin hydrochloride [49,50,51]

Chemical Structure



Category

Antidiabetic (Biguanides)

Chemical name

1,1-Dimethylbiguanide hydrochloride

Empirical formula

$C_4H_{11}N_5$, HCL

Molecular Weight

165.63 g/mol

Description

Nature

White to off white crystalline powder; hygroscopic.

Solubility

Freely soluble in water 300mg/ml at 2°C.

Practically insoluble in acetone, ether & chloroform.

pKa

The pKa of Metformin is 12.4

pH

The pH of a 1% aqueous solution of Metformin Hydrochloride is 6.68

Storage

Protected from light and moisture

Pharmacokinetic data

Bioavailability

50-60%

Metabolism

None

Half life

Plasma half life: 1.5-3 hours

Elimination half life: 6.2 hours

Distribution

654-358 L

Excretion

Active renal tubular secretion.

Pharmacological action

Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects

are mediated by the initial activation by Metformin of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, and the metabolism of glucose and fats. Activation of AMPK is required for Metformin inhibitory effect on the production of glucose by liver cells.

Clinical benefits of Metformin hydrochloride

Metformin hydrochloride is effective in the treatment of polycystic ovary disease. Its ability to lower insulin resistance in these women can result in ovulation and possibility for pregnancy.

Dose

250-1000 mg

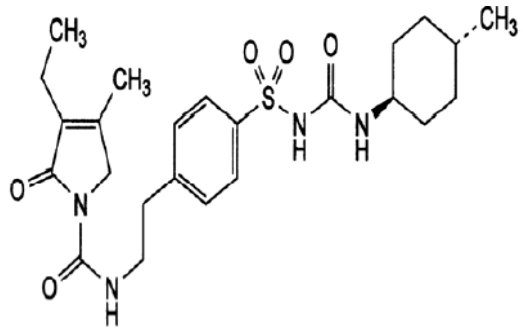
Table No - 3

Marketly available drug of Metformin hydrochloride

Brand name	Dose	Company name
Atformin	500mg	Active HL
Bigesens	500mg	Zydus carila
G-red SR tab	250mg	Orchid
Formin	500mg	Alkem

3.1.2 Glimepiride [7,50,51]

Chemical Structure



Category

Antidiabetic (Sulfonylurea)

Chemical name

1-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)-ethyl]phenyl]sulphonyl]-3-trans-(4-methylcyclohexyl)urea

Empirical formula

$C_{24}H_{34}N_4O_5S$

Molecular Weight

460.62

Description

Nature

White crystalline powder

Solubility

Freely soluble in dimethyl foramide, Acetonitrile. Slightly soluble in weak acid and base.

Storage

Store in a well closed containers, at a temperature not exceeding 25°C

Pharmacokinetic data

Bioavailability

Completely (100%) absorbed following oral administration.

Metabolism

Hepatic metabolism. glimepiride is completely metabolized by oxidative biotransformation

Half life

5-7 hours

Distribution

19.8 ± 12.7 L [Single Dose]

37.1 ± 18.2 L [Multiple Dose]

Excretion

Hepatic (biliary excretion)

Pharmacological action

The pharmacological of action of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells, and increasing sensitivity of peripheral tissues to insulin. Glimepiride likely binds to ATP-sensitive potassium channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Membrane depolarization stimulates calcium ion influx through voltage-sensitive calcium channels. This increase in intracellular calcium ion concentration induces the secretion of insulin.

Clinical benefits of Glimepiride

Best achieving the hypoglycemic effect.

Dose

1-2 mg/day

Table No : 4

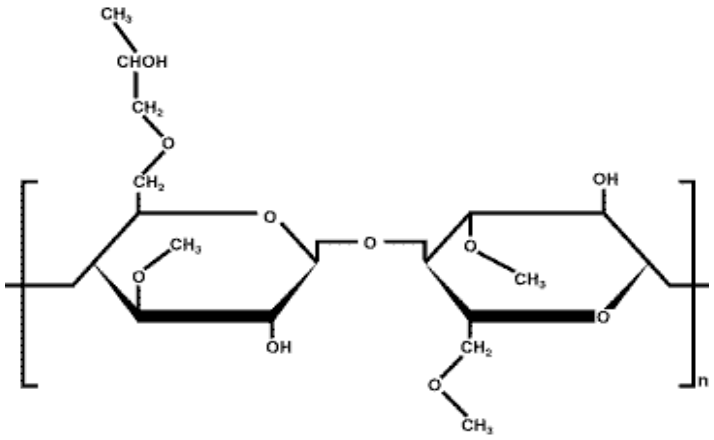
Marketed available Glimepiride

Brand name	Dose	Company name
Amaryl-fc tab	1mg	Sanofi Aventis
Azulix	1mg	Torrent
Chempride	1mg	chemch
Glimtide	1mg	Orchid
Glimpid	1mg	Ranbaxy

3.2 Execipients profile[52]

3.2.1 Hydroxy Propyl Methyl Cellulose (HPMC)

Chemical structure



Molecular Formula

$[C_6H_7O_2(OH)_{3-}(OCH_3)\text{-}(OCH_3CH(OH)\text{-}CH_3)]_n$

Synonym

Methyl hydroxyl propyl cellulose, Methyl cellulose, Propylene glycol ether.

Chemical name

Cellulose 2-hydroxy propyl methyl ether.

Non Proprietary Name

BP : Hypermellose

USP : Hydroxy Propyl Methyl Cellulose.

Molecular Weight

Approximately 86,000.

Category

Tablet binder, film former, coating agent, suspending agent, stability agent.

Description

White (or) Yellowish white fibrous (or) granular powder, almost odorless, hygroscopic after drying.

Solubility

Soluble in mixtures of ethanol & methylene chloride, practically insoluble in hot water, acetone, ethanol, toluene & ether. It swells in cold water forming an opalescent viscous colloidal solution.

Properties

- **Resistance to salting out**: HPMC is nonionic cellulose ether and it is not a polyelectrolyte. The aqueous solution of HPMC is comparatively stable even in the presence of metal salts or organic electrolytes. However, when the concentration of electrolytes exceeds a certain limit, gelation and precipitation may result.
- **Surface activity**: An aqueous solution of HPMC has a high surface activity and functions as a protective colloid agent, emulsion stabilizer and dispersant.
- **Thermal gelation:** An aqueous solution of HPMC will gel or precipitate when heated to a certain temperature, but it reverts to the original solution state on Subsequent cooling. The temperature at which gelation or precipitation occur depends on the type of HPMC, its concentration and the rate of heating.
- **pH stability**: The viscosity of an aqueous solution of HPMC is hardly affected by acid or alkali, and the product can develop an original viscosity

in the range of3.0~11.0. Therefore, the solution viscosity tends to keep stable during prolonged storage.

- **Water retention**: HPMC is a high effective water retention agent. Its pharmaceutical grade product can be widely used in food, cosmetics and many other fields.
- **Film forming**: HPMC provides a strong, flexible and transparent film having a good barrier property against oil and grease. In food application, this property is often utilized for water retention and oil adsorption.
- **Cohesiveness (Binding property):** HPMC, as a high performance binder, can also be used for molding food and medicine.

Specific Properties

Melting point

190-200°

Acidity/Alkalinity

5.5-8.0 for 1% w/w aqueous solution

Specific Gravity

1.26

Density

0.25-0.71 g/cm^3.

Viscosity grades

Commercially available viscosity grades are distinguished by a number indicative of apparent viscosity in millipascal seconds in 2% w/v solution at 20°.

Grades	Viscosity (cps)
HPMC K4M	4000
HPMC E-5	5
HPMC E-15	15

Application

Uses	Concentration (%)
Extended release Matrix formulation	15-35
Tablet Binder	2-6
Tablet film coating	2-20

- HPMC was used in the treatment of tear deficiency.
- It was a versatile and non-creative granulating agent.
- It swells in water & in virtually in all GIT fluids and it may expect to retard disintegration & dissolution time of drugs in the resulting tablets when wet granulation is employed.

Stability & Storage

Bulk material is stored in an air tight container and in cold & dry place. Increase in temperature decrease the viscosity of the solution.

Safety

HPMC was regarded as non-toxic & non-irritant, although excessive consumption causes laxative effect.

3.2.2 Sodium Bicarbonate

Chemical structure

$NaHCO_3$

Synonym

Sodium Hydrogen Carbonate, Monosodium carbonate, Sodium Acid Carbonate.

Chemical Name

Carbonic acid monosodium salt

Non-Proprietary Name

BP : Sodium Bicarbonate

USP : Sodium Bicarbonate

Molecular Weight

84.01

Category

Alkalizing agent, Therapeutic agent.

Description

Odorless, white, Crystalline powder with a saline, slightly alkaline taste.

Solubility

Practically insoluble in ethanol and ether

Soluble in water.

Typical properties

Acidity/ Alkalinity

pH=8.3 for a freshly prepared 0.1M aqueous solution at 25°C, alkalinity increases on standing, agitation or heating.

Density

0.869-2.173 g/cm^3

Freezing point depression

0.381°C

Melting point

270°C

Moisture content

Below 80% relative humidity, the moisture content is less than 1%w/w. Above 85% relative humidity, sodium bicarbonate rapidly absorbs excessive amounts of water and may start to decompose with loss of carbon dioxide.

Osmolarity:

1.39%w/v aqueous solution is isotonic with serum.

Refractive index

1.3344

Applications

Generally used as a source of carbon dioxide in effervescent tablet and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. Therapeutically, sodium bicarbonate may be used as an antacid and as a source of the bicarbonate anion in the treatment of metabolic acidosis. It is also used as a component of oral rehydration salts.

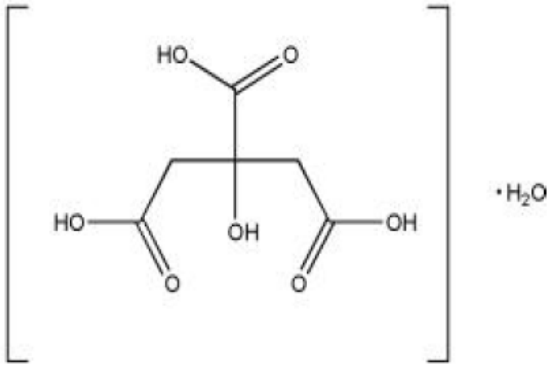
Table No : 5

Pharmaceutical application of Sodium Bicarbonate

Uses	Concentration (%)
Buffer in tablets	10-40
Effervescent tablet	25-50
Isotonic injection/infusion	1.39

3.2.3 Citric acid

Chemical structure



Synonym

2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

Chemical Name

2-Hydroxy-1,2,3-propanetricarboxylic acid monohydrate

Nonproprietary Names

BP : Citric acid monohydrate

USP : Citric acid

Molecular Weight

210.14

Category

Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer.

Description

It is colorless or translucent crystals or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is Orthorhombic.

Solubility:

Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.

Typical Properties

Acidity/alkalinity:

pH = 2.2 (1% w/v aqueous solution)

Dissociation constant:

p*K*a1	:	3.128 at 25°C;
p*K*a2	:	4.761 at 25°C;
p*K*a3	:	6.396 at 25°C.

Density:

1.542 g/cm3

Heat of combustion:

-×1972 kJ/mol (-×471.4 kcal/mol)

Heat of solution:

-¼16.3 kJ/mol (-¼3.9 kcal/mol) at 25°C

Hygroscopicity:

At relative humidities between about 65% and 75%, citric acid absorbs insignificant amounts of moisture, but under more humid conditions substantial amounts of water are absorbed.

Melting point:

100°C (softens at 75°C)

Viscosity (dynamic):

6.5 mPa s (6.5 cP) for a 50% w/v aqueous solution at 25°C.

Stability and Storage Conditions

Citric acid loses water of crystallization in dry air or when heated to about 40°C. It is slightly deliquescent in moist air. Dilute aqueous solutions of citric acid may ferment on standing.

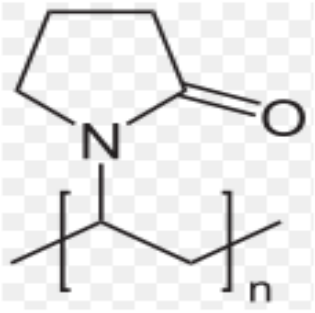
The bulk monohydrate or anhydrous material should be stored in airtight containers in a cool, dry place.

Safety

Orally ingested citric acid is absorbed and is generally regarded as a nontoxic material when used as an excipient. However, excessive or frequent consumption of citric acid has been associated with erosion of the teeth.

3.2.4 Povidone

Chemical structure



Molecular Formula

C_6H_9NO

Synonyms

Kollidon; plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone;pvp; 1-vinyl-2- pyrrolidinone polymer

Chemical name

1-ethenyl-2-pyrrolidinone homopolymer

Non proprietary name

Bp : povidone

Usp : povidone

Molecular weight

2500-3000000

Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

Description

Povidone occurs as a fine, white to creamy-white coloured, odourless or almost odourless ,hygroscopic powder. Povidones with k- values equal to or lower than 30 are manufactured by spray- drying and occur as spheres.

Solubility

Freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the k-value.

Typical Properties

Density (bulk)	:	0.29-0.39g/cm3
Density (tapped)	:	0.39-0.54g/cm3
Density (true)	:	1.180g/cm3

Melting point:

Softness at 1500c

Moisture content:

Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Stability &storage

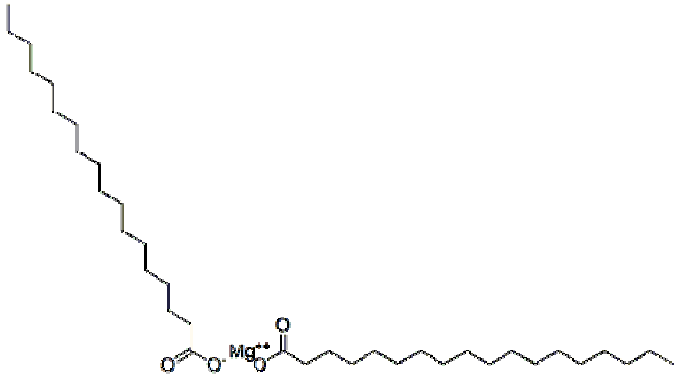
Povidone may be stored under ordinary conditions without under going decomposition or degration. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Safety

Povidone may be regarded as essentially nontoxic. Povidone additionally has no irritant effect on the skin and causes no sensitization.

3.2.5 Magnesium Stearate

Chemical Structure



Synonym

Stearic acid Magnesium salt, Magnesium Octadecanoate metallic stearate.

Chemical Name

Octadecanoic acid Magnesium salt.

Non-Proprietary Name

BP/ USPNF **:** Magnesium stearate

Molecular formula

$C_{36}H_{10}MgO_4$

Molecular Weight

591.27.

Category

Tablet & Capsule Ant adhesive, Lubricant & Glidant.

Description

Fine, White precipitated, milled, impalable powder of low bulk density having a faint characteristic odor and taste, poorly flowing cohesive powder, greasy to touch and adheres to skin.

Solubility

Insoluble in ethanol (95%) & water. Soluble slightly in warm benzene & hot alcohol.

Properties

Density

1.03-1.08 g/cm^3.

Melting point

361 K / 88°C

Storage & Stability

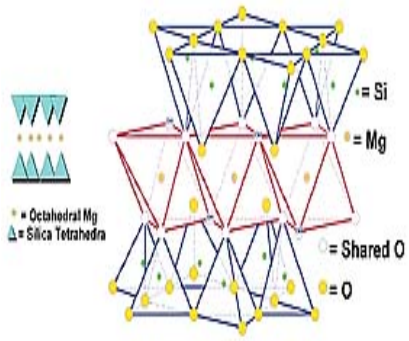
Magnesium Stearate is non-toxic following oral administration while inhalation is harmful.

Applications

- Magnesium Stearate is primarily used as lubricant in tablet & capsule manufacturing at 0.25-5% concentration.
- Used in cosmetics to prepare barrier creams.

3.2.6 Talc

Chemical Structure



Synonym

Hydrous magnesium calcium silicate; hydrous magnesium silicate

Chemical Name

Talc

Non-Proprietary Name

BP : purified talc

USP : talc

Molecular formula

Mg6 (Si2O5)4(OH)4.

Molecular Weight

379.27 gm

Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Solubility

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Properties

Acidity/alkalinity

pH = 7–10 for a 20% w/v aqueous dispersion.

Hardness (Mohs)

1.0–1.5

Moisture content

Talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Specific gravity

2.7–2.8

Storage & Stability

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour.

Talc should be stored in a well-closed container in a cool, dry place.

Applications

It is widely used in solid dosage forms as a Glidant and Lubricant.

Table No : 6

Application of Talc

Uses	Concentration
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0

4.1 AIM AND OBJECTIVE

- The aim of the present work is to formulate and evaluate Bilayer Floating tablets of Metformin HCl and Glimepiride for the treatment of Type 2 Diabetes Mellitus.
- To formulate Metformin HCl as sustained release layer and Glimepiride as immediate release layer.
- To formulate and evaluate sustained release layer by using Hydrophilic polymers like HPMC K4M, HPMC E-5 and HPMC E-15.
- To formulate and evaluate sustained release layer by using combined Hydrophilic polymers like HPMC K4M+HPMC E-5, HPMC E-5+HPMC E-15, HPMC K4M+HPMC E-15.
- Individual tablet were formulated and optimized separately by *in vitro* studies.
- To study the effect produced by employing various viscosity grades of Hydrophilic polymer
- Reduce dose frequency.
- Economically cheaper.
- Reduce pill burden.
- Providing easy medication.
- Improve patient compliance.

Need for present study

In Type2 Diabetes Mellitus patient Sulphonylureas and the Biguanide are the two most commonly used prescribed drugs for oral treatment.

In Sulphonylureas, Glimepiride were mostly prescribed drug because due to its low dosage (1-2mg) and its potent activity on glycemic control. In Biguanide, Metformin HCl are mostly prescribed drug, since it is an older and effective drug for maintaining blood glucose level.

Combination of Metformin HCl and Glimepiride were found to be very useful in Type 2 Diabetes Mellitus when compared with treatment of Metformin HCl and Glimepiride alone. In combination drug therapy, the blood glucose level is maintained in a very good manner.

The floating technique was employed to improve their absorption by increasing their gastric residence time and to reduce the unabsorbed drug (wastage of drug). Metformin HCl and Glimepiride is the drug, which does not cause any irritation on Gastric intestinal tract (GIT), and its absorption takes place in the upper part of the intestine.

From the above consideration the Metformin HCl and Glimepiride are suitable drugs for combination treatment of type 2 diabetes mellitus and to formulate as floating bilayer tablets.

5. PLAN OF WORK:

1. Preformulation studies:

- Active pharmaceutical ingredient characterization such as description, etc,
- Identification of absorption maxima of the drug by UV.
- Assessment of compatibility among formulation excipient by FT-IR analysis.

2. Formulation development

Development of sustained release layer tablets:

- Sustained release layer by using synthetic Hydrophilic polymer of different viscosity grade of same polymer.
  i.e.,Metformin hydrochloride +HPMC K4M
  Metformin hydrochloride +HPMC E-5
  Metformin hydrochloride +HPMC E-15

- Sustained release by using combined hydrophilic polymer of different grades.
  Metformin hydrochloride+ HPMC K4M+ HPMC E-5
  Metformin hydrochloride+ HPMC K4M+ HPMC E-15
  Metformin hydrochloride+ HPMC E-5+ HPMC E-15

Development of immediate release layer tablets:

- Immediate release by using disintegrant
  i.e.,Glimepride+povidone

3. Optimization of sustained release formulae by optimizing variables and polymer concentration for the development of Bilayer tablet.

4. Evaluation of formulation

a) Precompression parameters

- Bulk Density
- Tapped Density
- Angle of Repose
- Carr's Index
- Hausner's Ratio

b) Physico-chemical characteristics of compressed Floating Bilayer tablets

- Weight variation
- Thickness
- Hardness
- Friability
- Floating lag time
- Total buoyancy time
- Drug content analysis

c) *In-Vitro* drug release

- Tablet dissolution profile

d) Comparison of Drug release kinetic profiles of different formulation.

i.e., curve fitting analysis or kinetic model analysis

5. Stability studies (as per ICH guidelines)

6. MATERIALS AND METHODS

6.1 LIST OF MATERIALS

Table No - 7

List of Materials Used

S.NO	Materials	Manufacturer
1.	Metformin hydrochloride	Gift sample obtained from force India pharmaceuticals, Chennai.
2.	Glimepiride	Gift sample obtained from force India pharmaceuticals, Chennai.
3.	HPMC K4M	Hi Pure fine industries, Chennai
4.	HPMC E-5	Hi Pure fine industries, Chennai
5.	HPMC E-15	Hi Pure fine industries, Chennai
6.	Carbopol	Loba chemie Private Ltd, Mumbai
7.	Sodium Bicarbonate	Nice chemicals Private Ltd, Kerala
8.	Citric Acid	Nice chemicals Private Ltd, Kerala
9.	Povidone	Nice chemicals Private Ltd, Chennai
10.	Di Calcium Phosphate	Nice chemicals Private Ltd, Kerala
11	Magnesium stearate	Nice chemicals Private Ltd, Kerala
12	Talc	Nice chemicals Private Ltd, Kerala

6.2 LIST OF EQUIPMENTS

Table No – 8

List of Equipments Used

S.no	Equipments	Manufacturer	Use
1	UV-Visible double beam spectrophotometer	Shimadzu UV 1700(Pharmaspec)	To measure the absorbance of the sample
2	Electronic Balance	Sartorius Single Pan	For weighing purpose
3	Rotary tablet punching machine	Rimek MiniPress-I	For tablet punching
4	Friabilator	Roche	For friability testing
5	Tablet Hardness tester	Monsanto	For testing hardness of the tablet
6	Programmable Dissolution test apparatus	Electro Lab (Tablet Dissolution tester USP 24)	For *in-vitro* dissolution studies
7	pH meter	Elico L 1120	To measure the pH of the solution
8.	Environmental stability testing chamber	Heco Environment Chamber	For stability studies
9.	FT-IR	Schimadzu IR – Prestige-21	For compatibility analysis

6.3 PREPARATION OF REAGENTS

6.3.1Preparation of 0.1N HCL

8.5 ml of Con.HCl dissolved in 1000ml of distilled water to prepare a 0.1N HCl.

6.3.2 Stimulated Gastric Fluid pH 1.2

0.2 gm sodium chloride and 0.7ml of concentrated hydrochloric acid were mixed, to this mixture 1000ml distilled water are added and the solution was adjusted to pH 1.2 with sodium hydroxide solution.

6.4 ABSORPTION MAXIMA AND STANDARD PLOTS

6.4.1 Preparation of Absorption maxima for Metformin hydrochloride using pH 1.2 stimulated gastric fluid.

Accurately weighed amount of Metformin hydrochloride (100 mg) was dissolved in small quantity of stimulated gastric fluid pH 1.2 and then diluted to 100 ml with the same solvent. Each ml of the stock solution contains 1 mg of Metformin hydrochloride. From this stock solution different standard of working standard solutions i.e., 10, 20, 30, 40, 50 µg/ml were made up with stimulated gastric fluid pH 1.2 and the absorbance was measured at 232nm using stimulated gastric fluid as blank by UV spectroscopic method[47]. A graph was plotted by using concentration at X-axis and absorbance at Y-axis.

Absorption maxima and UV spectrum of Metformin hydrochloride

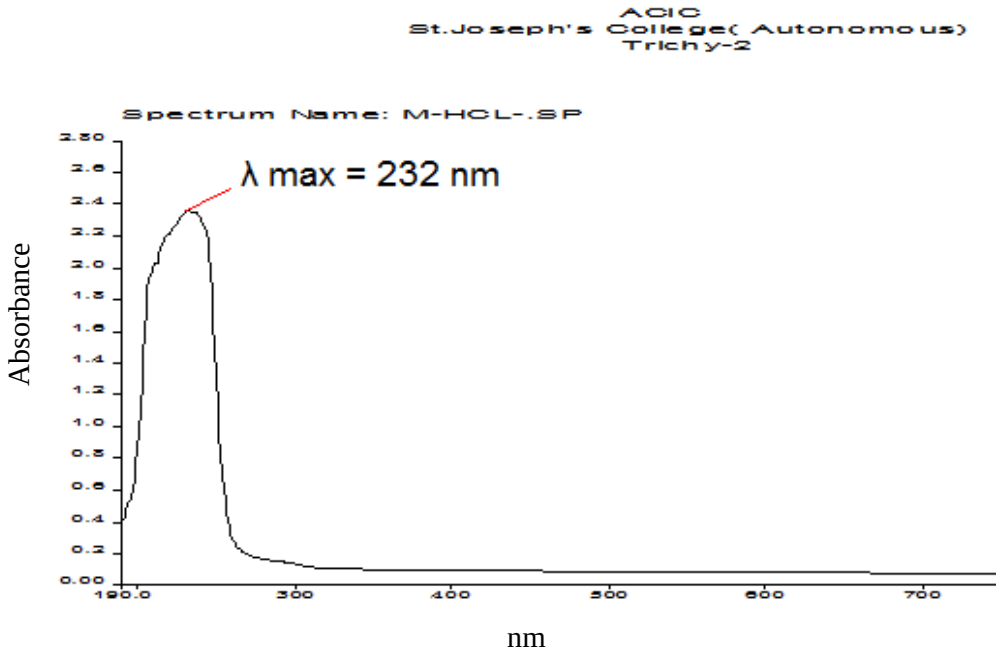


Fig : 5

6.4.2 Standard Plot

6.4.2.1 Standard plot of Metformin hydrochloride in stimulated gastric fluid pH 1.2

Table No: 9

Standard plot of Metformin HCl

S.No	Concentration µg/ml	Absorbance at 232nm
1	0	0
2	10	0.2897
3	20	0.5371
4	30	0.8484
5	40	1.118
6	50	1.39

Standard plot of Metformin hydrochloride in stimulated gastric fluid pH1.2

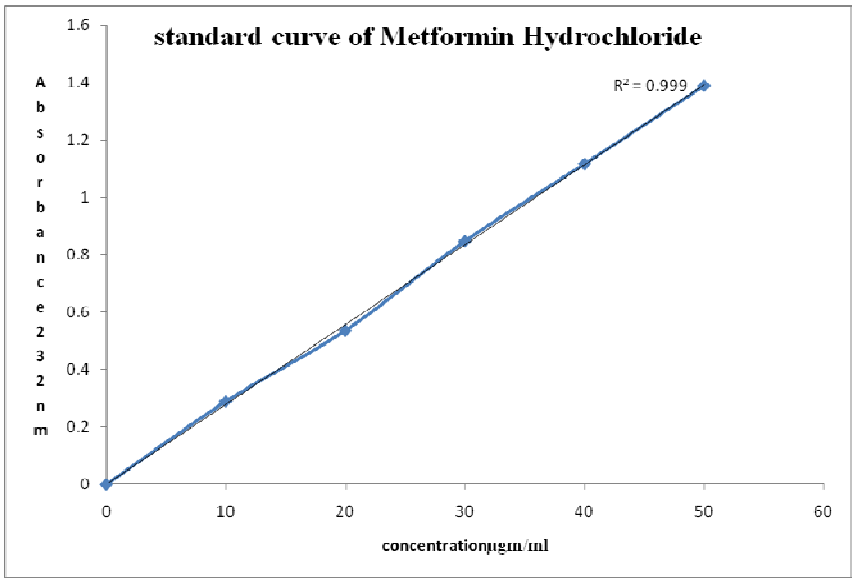


Fig : 6

6.4.3 Preparation of Absorption maxima for Glimepiride using pH 1.2 stimulated gastric fluid.

Accurately weighed amount of Glimepiride (100 mg) was dissolved in small quantity of acetonitrile and then diluted to 100 ml with stimulated gastric fluid pH 1.2. Each ml of the stock solution contains 1 mg of Glimepiride. From this stock solution different standard of working standard solutions i.e., 10, 20, 30, 40, 50 µg/ml were made up with stimulated gastric fluid pH 1.2 and the absorbance was measured at 226.7nm using stimulated gastric fluid as blank by UV spectroscopic method[53]. A graph was plotted by using concentration at X-axis and absorbance at Y-axis.

Absorption maxima and UV Spectrum of Glimepride

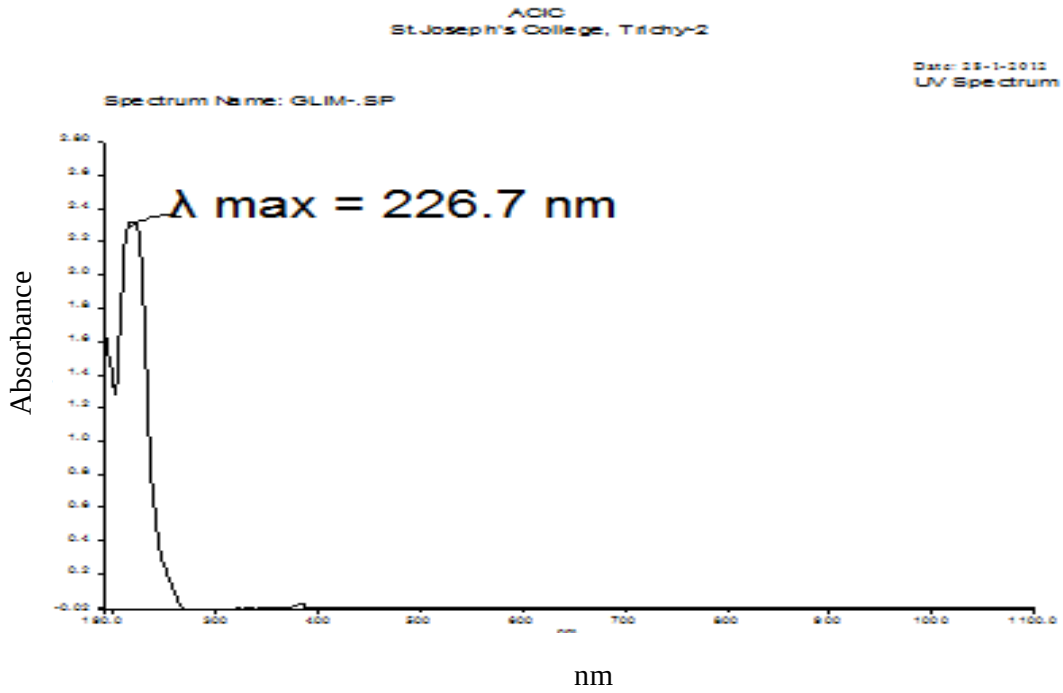


Fig : 7

Standard Plot

6.4.4 Standard plot of Glimepiride in stimulated gastric fluid pH 1.2

Table No : 10

Standard curve of Glimepiride

S.No	Concentration µg/ml	Absorbance at 226.7nm
1	0	0
2	10	0.231
3	20	0.469
4	30	0.700
5	40	0.941
6	50	1.145

Standard plot of Glimepiride in stimulated gastric fluid pH1.2

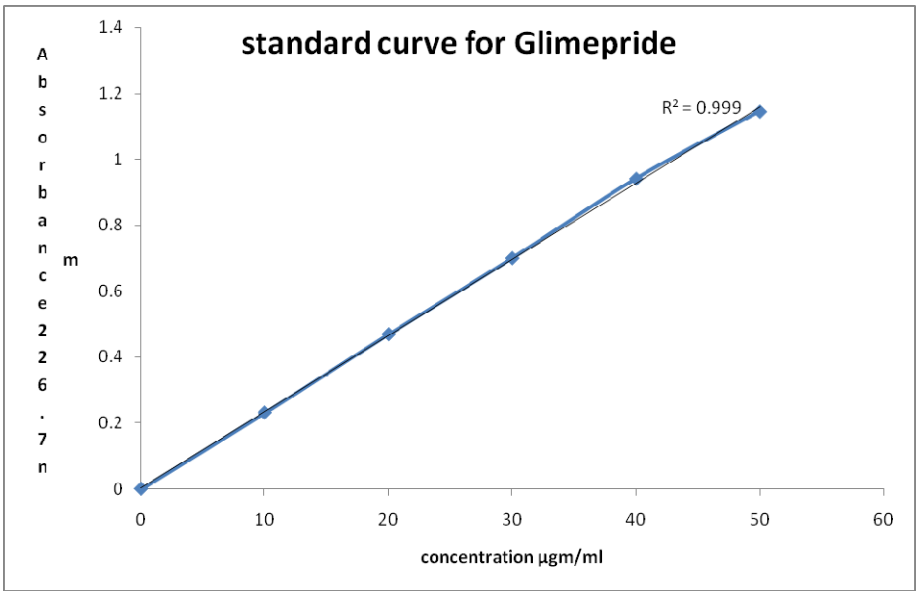


Fig : 8

7. PREFORMULATION STUDIES

Preformulation may be described as a stage of development process during which the researches characterize the physical, chemical and mechanical properties of the drug substance to form effective, stable and safe dosage form. Hence, Preformulation studies are essential to characterize the drug for proper designing of the drug delivery system. The Preformulation studies that were performing in this project include,

- Description
- Drug – excipient compatibility studies
- Assay

7.1 Description

Organoleptic characters of drug was observed and recorded by using descriptive terminology.

7.2Drug-Excipient Compatibility Studies by FT-IR Analysis

Infrared spectrum of any compound or drug gives information about the groups present in that particular compound. The IR absorption spectra of the pure drug and physical admixtures of drug with various excipients were taken in the range of 4000-400 cm^{-1} using KBr disc method (Schimadzu IR- Prestige-21) and observed for characteristic peaks of drug.

7.3 Assay

A. For Metformin hydrochloride

Weigh accurately a quantity of the powder containing about 0.1g of Metformin hydrochloride, shake with 70ml of water for 15 minutes, make up to 100ml with water, and filter. Dilute 10ml of the filtrate to 100ml with water. Further 10ml of the filtrate were make up to 100ml with water and measure the absorbance of the resulting solution at the maximum about 232nm. Calculate the content of $C_4H_{11}N_5$, HCl taking 798 as the specific absorbance at 232nm.

B. For Glimepiride

Twenty tablets from each batch were weighed and powdered. Powder equivalent to 4mg of Glimepiride was accurately weighed and transferred into 100ml volumetric flask and dissolve in acetronitrile until clear solution is obtained. The resulting solutions was made to 100ml with 0.1N HCl and shake for 10 mins. The 10ml of the above solution was diluted up to 100ml with 0.1N HCl and flitered through 0.45µ membrane fliter analyzed by Shimadzu UV/VIS double beam spectrometer at 226.7nm.

8. FORMULATION & EVALUATION

8.1 Formulation Development

The pharmaceutical development studies have to be carried out with the purpose of selecting right dosage form and a stable formulation. These studies give detailed description of all the steps involved in the process development of Bilayer Floating tablet. Such details are intended towards identifying critical parameters involved in the process, which have to be controlled in order to give reliable and reproducible quality product.

8.1.1 Formulation of floating Bilayer Tablet

The floating Bilayer tablet was prepared by direct compression method.

Steps involved in Bilayer Tablet Preparation

1. Filling of immediate release layer of Glimepiride granules in to dies
2. Slightly compressed the immediate release layer of Glimepiride granules
3. Ejection of upper punch
4. Addition of floating sustained release layer of Metformin hydrochloride granules over the immediate release granules
5. Increasing the compression force and compressed both the layer
6. Ejection of floating Bilayer tablet

A. Preparation of Floating Metformin HCl Sustained Release (SR)

Drug (Metformin hydrochloride) + Polymer (HPMC K4M, HPMC E-5, HPMC E-15)

↓

Gas generating agents (Sodium bicarbonate + citric acid) + Carbopol + Povidone

↓

Dry granules were passed through a mesh no: 44

↓

Mixed with magnesium stearate, talc

↓

Compression

B. Preparation of Glimepiride Immediate Release (IR)]

Drug (Glimepiride) + Povidone

↓

Dicalcium Phosphate (filler) + coloring agent

↓

Dry granules were passed through a mesh no: 44

↓

Mixed with magnesium stearate, talc

↓

Compression

8.1.2 Consideration for Formulation Development

- Formulation Development of Floating sustained release layer (MetforminHCl) by optimizing polymer concentration
- Optimization of immediate release layer (Glimepiride) by variables.
- Formulation of floating Bilayer tablet from optimized formula on the basis of *in-vitro* studies.

8.1.3 Trial Formulations

Different formulation trial batches of Floating Metformin HCl SR and Glimepiride IR were formulated and studied for their release profiles to get the optimized formulation of Floating Bilayer tablet.

8.1.3.1Formulation Trial Batch of Floating Metformin HCl SR Tablet

The trial batch of Floating Metformin HCl SR was prepared by employing drug with varying the percentage of polymers like HPMC E-15, HPMC E-5, HPMC K4M. It was shown in the table (11). Different percentage of polymers have been used in trial batch and studied to have Metformin HCl sustaining effect for period of 20 hours.

Table No - 11

Formulation Trial Batch of Floating Metformin HCl SR (HPMC E-15)

S.No	Ingredients	Formulation code (amount per tablet in mg)			
		M1	**M2**	**M3**	**M4**
1	Metformin HCL	250	250	250	250
2	**Polymer concentration (%)**	**20**	**40**	**60**	**80**
3	HPMC E-15	50	100	150	200
4	Carbopol 934	100	100	100	100
5	Sodium bicarbonate	100	100	100	100
6	Citric acid	50	50	50	50
7	Povidone	50	50	50	50

Table No - 12

Formulation Trial Batch of Floating Metformin HCl SR (HPMC E-5)

S.No	Ingredients	Formulation code (amount per tablet in mg)			
		M5	**M6**	**M7**	**M8**
1	Metformin HCL	250	250	250	250
2	**Polymer concentration (%)**	**20**	**40**	**60**	**80**
3	HPMC E-5	50	100	150	200
4	Carbopol 934	100	100	100	100
5	Sodium bicarbonate	100	100	100	100
6	Citric acid	50	50	50	50
7	Povidone	50	50	50	50

Table No - 13

Formulation Trial Batch of Floating Metformin HCl SR (HPMC K4M)

S.No	Ingredients	Formulation code (amount per tablet in mg)			
		M9	**M10**	**M11**	**M12**
1	Metformin HCL	250	250	250	250
2	**Polymer concentration (%)**	**20**	**40**	**60**	**80**
3	HPMC K4M	50	100	150	200
4	Carbopol 934	100	100	100	100
5	Sodium bicarbonate	100	100	100	100
6	Citric acid	50	50	50	50
7	Povidone	50	50	50	50

Weight of active ingredient = 250mg

Total weight of the tablet = 600mg

8.1.3.2 Formulation Trial Batch of Glimepiride Immediate Release (IR) Tablet

The trial batch of Glimepiride IR tablet containing drug Glimepiride with disintegrant was prepared according to the following formula. Different percentage of disintegrant has been used in trial batch and to study the immediate release effect of Glimepiride. It was shown in the following table (14).

Table No - 14

Formulation Trial Batch of Glimepiride IR

Ingredients	Formulation code (amount per tablet in mg)			
	G1	**G2**	**G3**	**G4**
Glimepiride	1	1	1	1
Povidone	**4**	**6**	**8**	**10**
Dicalcium phosphate	38.98	38.98	38.98	38.98
Magnesium stearate	1%	1%	1%	1%
Talc	1%	1%	1%	1%

Weight of active ingredient = 1mg

Total weight of active ingredient = 50mg

8.1.3.3Formulation of Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR

From the trial formulations of Floating Metformin HCl SR and Glimepiride IR, the Bilayer floating tablet of Metformin HCl SR and Glimepiride IR are formulated by varying the percentage of polymers.

Table No – 15

Percentage of polymer used

Formulation code	Percentage of polymer
C1,C4,C7	20&60%
C2,C5,C8	40&40%
C3,C6,C9	60&20%

Table No - 16

Formulation of Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR

S.No	Ingredients	Formulation code (amount per tablet in mg)								
		C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
1	Metformin HCl	250	250	250	250	250	250	250	250	250
2	HPMC K4M	50	100	150	-	-	-	150	100	50
3	HPMC E-15	150	100	50	50	100	150	-	-	-
4	HPMC E-5	-	-	-	150	100	50	50	100	150
5	Carbopol 934	100	100	100	100	100	100	100	100	100
6	Sodium Bicarbonate	100	100	100	100	100	100	100	100	100
7	Citric Acid	50	50	50	50	50	50	50	50	50
8	Povidone	60	60	60	60	60	60	60	60	60
9	Glimepiride	1	1	1	1	1	1	1	1	1
10	Povidone	10	10	10	10	10	10	10	10	10
11	Dicalcium Phosphate	38.9	38.9	38.9	38.9	38.9	38.9	38.9	38.9	38.9
12	Magnesium Stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%
13	Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%

Weight of active ingredient = 250mg

Total weight of tablet = 650mg

8.2 EVALUATION PARAMETER

Trial batches of different formulations of individual tablets (sustained and immediate) and Bilayer tablets were prepared and evaluated for the following parameters.

Evaluation of granules

- Bulk Density
- Tapped Density
- Angle of Repose
- Carr's Index
- Hausner's Ratio

Physical evaluation of tablet

- Weight variation
- Thickness
- Hardness
- Friability
- Swelling index
- Floating lag time
- Total buoyancy time
- Drug content analysis

***In-Vitro* drug release study**

- Tablet dissolution profile

Stability studies (As per ICH guidelines)

8.2.1 Evaluation of Granules[51]

The ideal characteristics of a tablet that makes it a popular and acceptable dosage forms when they are compactness, physical stability, rapid production capability, chemical stability and efficacy. Many formulation and process variables involved in the granulation step can affect the characteristics of the granules. Therefore various granulation characteristics such as flow property, compressibility index have been measured to monitor the granulation stability**.**

8.2.1.1Angle of repose

The angle of repose is defined as the maximum angle possible between the surface of a pile powder and the horizontal plane. The tangent of the angle is equal to the coefficient of friction between the particles.

$$\tan\theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where, h = height of the pile

r = radius of the pile.

Procedure

A funnel is fixed at particular height 'h' cm on a burette stand. A white paper is placed below the funnel on the table. The given powdered drug whose angle is to be determined is passed slowly through the funnel, until it forms a pile, care is taken to see that the drug particulars slip and roll over each other through the sides of the funnel. Circumference of the pile of drug is drawn with a pencil and the height of the pile was measured without disturbing the pile. The radius of the pile is noted down as 'r' cm. Angle of repose of the drug is then calculated by using the formulae. Standard value for flow property was shown in the table

Table No - 17

FLOW PROPERTIES AND CORRESPONDING ANGLE OF REPOSE

Flow Property	Angle of Repose (°)
Excellent	25-30
Good	31-35
Fair – aid not needed	36 – 40
Passable – may hang up	41 – 45
Poor – mast agitate, vibrate	46 – 55
Very poor	56 – 65
Very, very poor	>66

8.2.1.2Bulk Density and Tapped Density

A measured quantity of granules was transferred to a measuring cylinder measuring its initial volume [V_0] and tapped mechanically either manually or using some tapping device till a constant volume [V_f] and it includes the true volume of the granules and void space between them. The bulk density and tapped density was calculated by the following formulae. Bulk density is the ratio between a mass of granules and its bulk volume (V_o). It is expressed by g/cc.

$$\text{Bulk Density} = \frac{\text{Mass of Powder}}{\text{Bulk Volume of Powder } (V_o)}$$

Tapped density is the ratio between mass of granules and volume of the granules after tapping (V_F). It is expressed by gm/cc.

$$\text{Tapped Density} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Powder } (V_F)}$$

8.2.1.3Compressibility Index and Hausner's Ratio

The compressibility index and Hausner's ratio are measures the flow property of a powder to be compressed. As such, they measure the relative importance as interparticulate Interactions. In a free flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in values. For poorer flowing materials, Inter particulate Interactions will be greater and greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's ratio.

The compressibility index and Hausner's ratio are calculated by measuring the values for bulk density (ρ bulk) and Tapped Density (ρ tapped) as follows, and official limits are shown in the table().

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table No - 18

Official Limits for Carr's Index

Carr's Index	Types of flow
5-15	Excellent
12-16	Good
18-23	Fair to pass
23-35	Poor
33-38	Very Poor
Above	Extremely Poor

Hausner's ratio is the measurement of frictional resistance of the drug and the ideal range should be 1.2-1.5 and the official limits are shown in table ().

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table No - 19

Flow Properties and Corresponding Hausner's Ratio

Hausner's Ratio	Types of flow
1-1.11	Excellent
1.12-1.18	Good
1.18-1.25	Fair
1.26-1.34	Passable
1.36-1.45	Poor
1.46-1.59	Very Poor
Above 1.6	Very Very Poor

8.2Physical Evaluation of Tablet[47]

8.2.1Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual weight deviates from the average weight by more than the percentage shown in the table no(20) and none should deviate by more than twice the percentage shown. The average weight and standard deviation of the tablets of each batch were given in the table.

Table no - 20

Weight Variation Specification (IP Limits)

Average weight of tablet (mg)	Percentage deviation
80 or less	10
80 to 250	7.5
More than 250	5

8.2.2Hardness

The tablet-crushing load is the force required to break a tablet by compression. Hardness was measured by using hardness tester (Pfizer hardness tester). For each batch, six tablets were selected randomly and evaluated. Hardness of about 4-6 kg/cm^2 is considered to be minimum for uncoated tablets and for mechanical stability.

8.2.3Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. Preweighed sample of ten tablets were placed in the friabilator, which was then operated for 100 revolutions. After 100 revolutions, the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

$$\text{Percentage Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} \times 100$$

8.2.4 Floating Lag Time

The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

8.2.5 Total Buoyancy Time

The time for which the tablets constantly float on the surface was determined as total buoyancy time.

8.2.6 Swelling Index

Swelling of tablet excipients (polymer) involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of percentage weight gain by the tablet.

Method

One tablet was weighed and placed in a beaker containing 200ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 5hrs. The %weight gain by the tablet was calculated by the formula,

Swelling index (S.I) = {(Wt-W0)/W0}*100

Where Wt = weight of tablet at time t,

W0 = weight of tablet before immersion.

8.2.7 Drug content analysis

For Metformin hydrochloride

Weigh accurately a Metformin hydrochloride, shake with 70ml of water for 15 minutes, make up to 100ml with water, and filter. Dilute 10ml of the filtrate to 100ml with water. Further 10ml of the filtrate were make up to 100ml with water and measure the absorbance of the resulting solution at the maximum about 232nm. Calculate the content of $C_4H_{11}N_5$, HCl taking 798 as the specific absorbance at 232nm.

For Glimepiride

Twenty tablets from each batch were weighed and powdered. Powder equivalent to 4mg of Glimepiride was accurately weighed and transferred into 100ml volumetric flask and dissolve in acetronitrile until clear solution is obtained. The resulting solutions was made to 100ml with 0.1N HCl and shake for 10 mins. The 10ml of the above solution was diluted up to 100ml with 0.1N HCl and flitered through 0.45µ membrane fliter analyzed by Shimadzu UV/VIS double beam spectrometer at 226.7nm.

$$\text{Percentage purity of Drug content} = \frac{\text{Amount of drug}}{\text{Label claim}} \times 100$$

$$\text{Amount of Drug} = \frac{\text{Sample OD}}{\text{A (1\% 1cm)}} \times \frac{\text{Sample Dilution}}{\text{Sample Weight}} \times \text{Average Weight}$$

$$\text{Sample Weight} = \frac{\text{Average weight}}{\text{Label claim}} \times \text{Equivalent weight}$$

8.2.5 In-Vitro Drug Dissolution Test[47]

The *in-vitro* dissolution study of Floating Metformin HCl SR tablet, Glimepiride IR tablet and optimized Bilayer Floating tablet of Metformin HCl SR and Glimepiride IR were performed according to USP apparatus II (Basket type). The following parameters are considered for the dissolution study.

Table No - 21

Parameters for *In-Vitro* Dissolution Study

Parameters	**Metformin HCl floating sustained release tablet**	**Glimepiride immediate Release Tablet**	**Bilayer Tablet of Floating Metformin HCl SR & Glimepiride IR**
Dissolution medium	Stimulated Gastric fluid pH1.2	Stimulated Gastric fluid pH1.2	Stimulated Gastric fluid pH1.2
Volume	900 ml	900 ml	900 ml
Rpm	50	50	50
Temperature	37º C ± 1º C	37º C ± 1º C	37º C ± 1º C
UV Absorbance Measurement	232 nm	226.7 nm	Simultaneously at 232 and 226.7 nm

The dissolution study was carried out for all the formulations and the best release profiles were compared using kinetic model

8.2.6Drug release kinetics[52]

Several theories and kinetic models describe the dissolution of drug from immediate release and modified release dosage forms. There are several models to represent the drug dissolution profiles where f (t) is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form.

The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically

translates the dissolution curve function of some parameters related with the pharmaceutical dosage forms. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time‘t’ or Q(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models. These models are used to characterize drug dissolution/release profiles.

(i) Zero Order Kinetics[53]

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (that is, a constant release rate). The following equation is used to express the model:

$$\mathbf{Q_t = Q_o + K_o t}$$

Where, Q_t is the amount of drug dissolved in time t

Q_o is the initial amount of drug in the solution

K_o is the zero order release constant

For practical purposes the equation is rearranged:

Percent drug released = Kt

This is applicable to dosage forms like transdermal systems, coated dosage forms, osmotic systems as well as matrix tablets with low soluble drugs.

(ii) First Order Kinetics[54]

First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior; in such a way that amount of drug released by unit time diminish. The following equation is used to express the model:

$$\log Q_t = \log Q_o + Kt/2.303$$

Where, Q_t is the amount of drug dissolved in time t

Q_o is the initial amount of drug in the solution

K is the first order release constant

For practical purposes the equation is rearranged:

Log % of drug unreleased = Kt/2.303

This model is applicable to dosage forms such as those containing water-soluble drugs in porous matrices.

(iii) Higuchi Model[55]

Higuchi describes drug release as a diffusion process based in Fick's law, square root dependent. The following equation is used to express the model:

$$Q_t = K_h t^{1/2}$$

Where, Q_t is the amount of drug dissolved in time t

K_h is the first order release constant

For practical purposes the equation is rearranged:

Percent drug released = $Kt^{1/2}$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drugs.

(iv) Peppas-Korsmeyer Model[56]

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved

The following equation is used to express the model

$$\mathbf{Q_t/Q_\infty = Kt^n}$$

Where, Q_t is the amount of drug dissolved in time t

Q_∞ is the amount of drug dissolved in infinite time

n is the release exponent indicative of drug release mechanism

K is the kinetic constant

For practical purposes the equation is rearranged:

Log percent drug released = log k +n log t

Peppas used n value in order to characterize different release mechanism concluding for values of n = 0.5 for Fickian diffusion and values of n, between 0.5 to 1.0 for anomalous transport (corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics) and higher values of n, n=1 or n>1 for case-II transport (corresponds to erosion and relaxation of swollen polymer layer).

8.2.7 Stability Study[57,58]

Stability is officially defined as the time lapse during which the drug product retains the same properties and characteristics that is possessed at the time of manufactures. This process begins at early development phases. Instabilities in modern formulation are often detected only after considerable storage periods under normal conditions. To reduce their time required to obtain information's, various tests that involve storage of products under condition that accelerate decomposition have been introduced. Stability storage condition shown in the table no(22).

ICH Guidelines – Specifications

- 5% potency loss from initial assay of batch
- Any specified degradation that exceed specifications
- Product failing out of pharmacopoeial limits.
- Dissolution out of specification for 12 minutes.
- Failure to meet specification for appearance and physical properties.

Any one condition is observed then stability of the batch is failed.

Table No: 22

STABILITY STORAGE CONDITIONS

S.No.	Study Period	Storage Condition	Minimum Duration
1	Longer	25 $\pm$ 2^{o} C 60 $\pm$ 5% RH	6 Months
2	Intermediate	30 $\pm$ 2 ^{o} C 60 $\pm$ 5% RH	3 Months
3	Accelerated	40 $\pm$ 2^{o} C 75 $\pm$ 5% RH	3 Months

The optimized bilayer floating tablets were packed in HDPE (high density poly ethylene) containers and kept in stability chamber at 40 ^{o} C/75% RH. After specific period of storage for stability, the tablets were evaluated for physical parameters, *in-vitro* drug release and assay.

9 RESULTS AND DISCUSSION

9.1 Preformulation studies

9.1.1 Description

Metformin hydrochloride : White to off white crystalline powder

Glimepiride : White crystalline powder

9.1.2 Drug- Excipient Compatibility Studies by FT-IR analysis

Drug-Excipient compatibility was carried out by FT-IR analysis. Initially the IR spectrum of pure drug, Metformin HCl and Glimepiride and excipients like HPMC K4M, HPMC E-5 and HPMC E-15 was obtained. After that various admixtures of drug with other excipients like Metformin HCl, Glimepiride, HPMC K4M, HPMC E-5 and HPMC E-15 were prepared and IR spectra were obtained. The obtained spectra of physical admixtures were observed for major peaks and recorded.

In Metformin HCl drug was noticed that C-N stretching at 3303.04 and C-H stretching at 2692.21 In Glimepiride drug was noticed that C-N stretching at 3370.34 and C-H stretching at 2856.80. In **combination of both the drugs** (Metformin HCl & Glimepiride) C-N stretching at 3289.10, C-H stretching at 2856.80 and C-H(out of plane) at 798.49. Functional group are more or less similar to that of individual pure drug.

In Metformin HCl was noticed that C-H stretching at 3171.90 and in Glimepiride drug was noticed that C-H aliphatic stretching at 2358.90. In **combination of Metformin HCl , Glimepiride and Polymer** were admixture and followed the same group in C-H stretching at 2939.64, 2944.65, 2940.92 and C-H aliphatic stretching at 2213.68, 2497.21, 2202.74. Functional group value are more or less similar that of individual pure drug.

In Metformin HCl was noticed that N-H stretching at 3376.04 and in Glimepiride drug was noticed that C=S stretching at 1445.72 In **combination of Metformin HCl , Glimepiride and Polymer** were admixture and followed the same group in N-H stretching at 3375.06,3385.45,3383.44 C=S stretching at1442.18, 1446.64,1451.54. Functional group value are more or less similar that of individual pure drug.

In Metformin HCl was noticed that C-H out of plane at 931.65 and in Glimepiride drug was noticed that S=O stretching at 1347.41. In **combination of Metformin HCl , Glimepiride and Polymer** were admixture and followed the same group in C-H out of plane at 936.80, 939.58,937 S=O stretching at 1351.27.

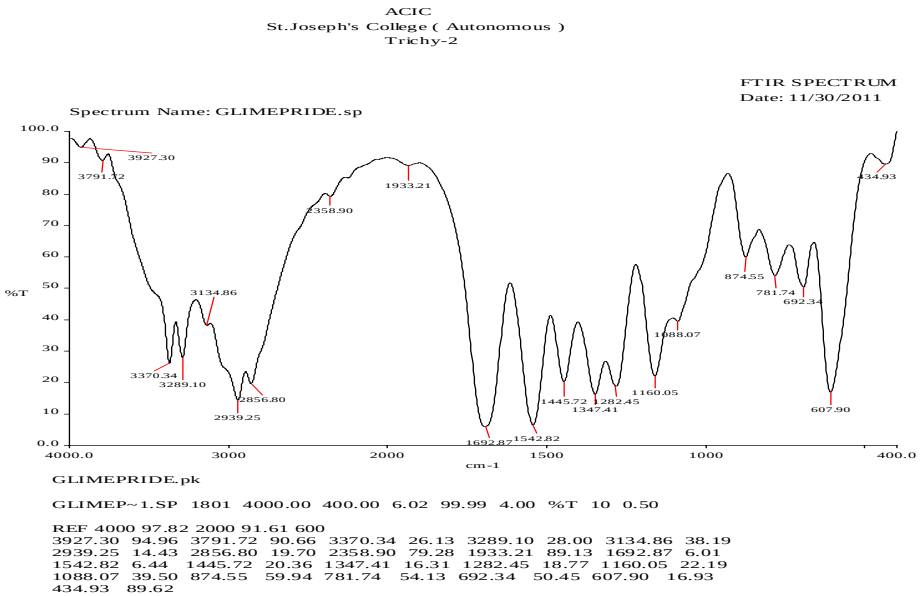


Fig : 9 IR Spectral assignment of Glimepiride

Table No : 23

IR Spectral assignment of Glimepiride

S.No	Wave number(cm^{-1})	Assignment
1	3370.34	N-H stretching
2	2939.25	C-H stretching(Aromatic)
3	2358.90	C-H stretching(Aliphatic)
4	1692.87	C=O stretching
5	1445.72	C=N stretching
6	1347.41	S=O stretching
7	1282.45	C-N stretching
8	1160.05	C=C stretching
9	874.55	C-H outplane bending

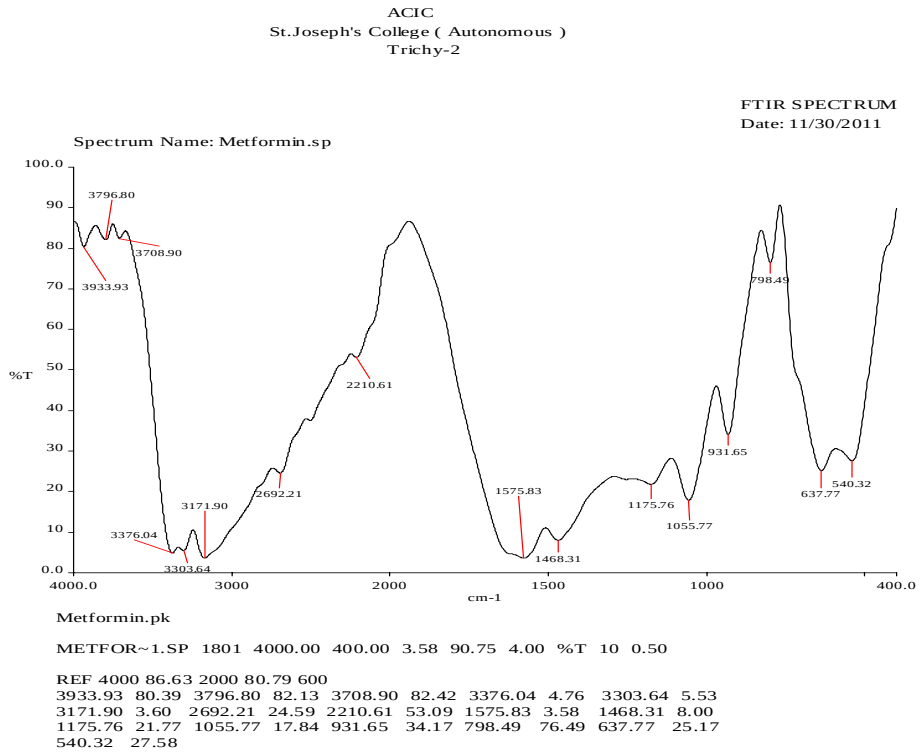


Fig : 10 IR Spectral assignment of Metformin HCl

Table No : 24

IR Spectral assignment of Metformin HCl

S.no	Wavenumber (cm^{-1})	Assignment
1	3173.06	N-H stretching
2	2687.10	C-H stretching
3	1629.52	C=O stretching
4	1573.03	C-N stretching
5	1168.15	C-C stretching
6	931.12	C-H out plane bending

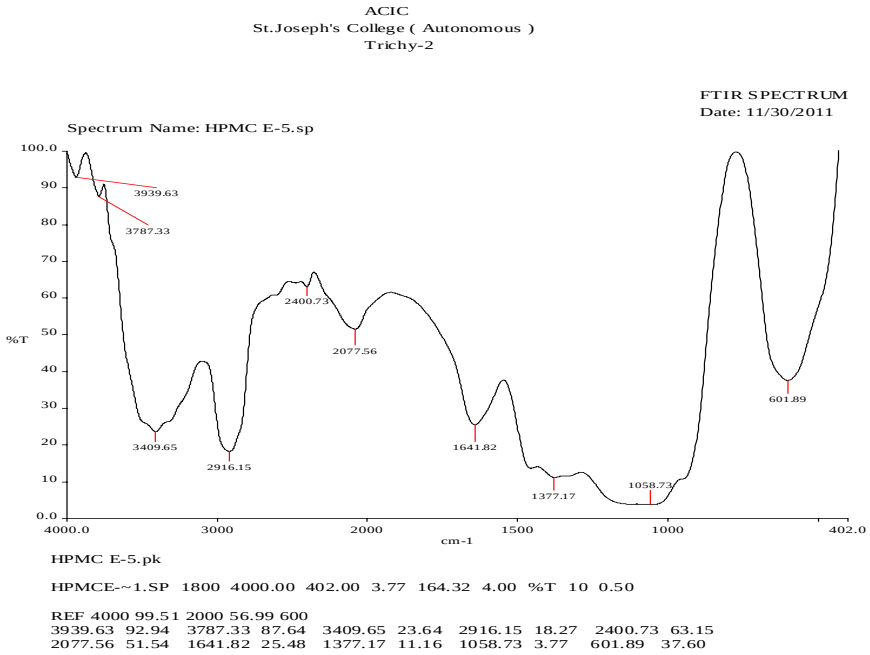


Fig : 11 IR Spectral assignment of HPMC E-5

Table No : 25

IR Spectral assignment of HPMC E-5

S.No	Wavenumber (cm^{-1})	Assignment
1	3409.65	O-H stretching (primary amine)
2	2916.15	C-H stretching
3	2077.56	C-H stretching (Aliphatic)
4	1641.82	C=O stretching (Isomeric carbonyl)
5	1377.17	C-O bend
6	1058.73	C-C bend
7	601.89	C-H out of plane

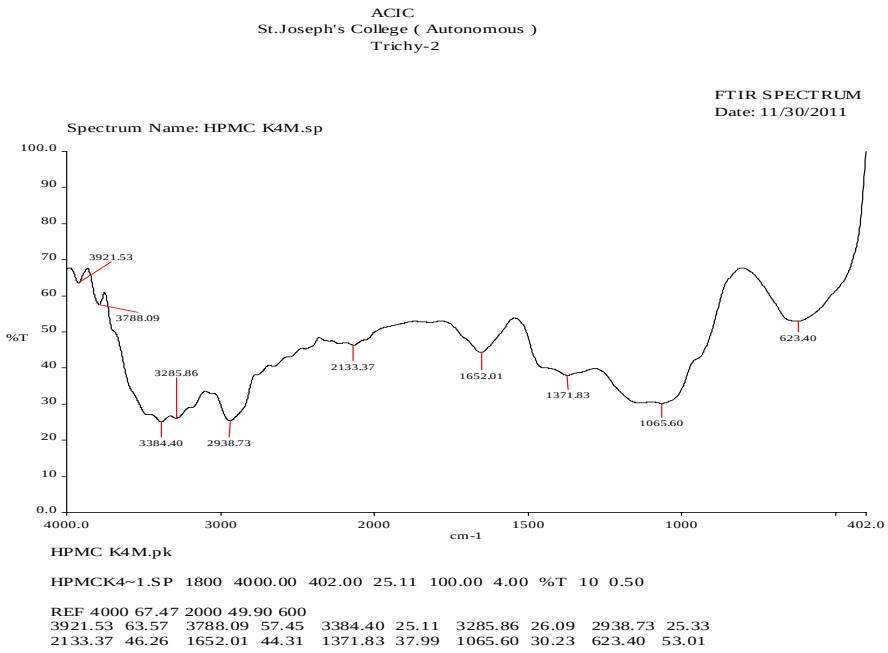


Fig : 12 IR Spectral assignment of HPMC K-4M

Table No : 26

IR Spectral assignment of HPMC K-4M

S.No	Wave number (cm^{-1})	Assignment
1	3409.65	O-H stretching (primary amine)
2	2916.15	C-H stretching
3	2077.56	C-H stretching (Aliphatic)
4	1641.82	C=O stretching (Isomeric carbonyl)
5	1377.17	C-O bend
6	1058.73	C-C bend
7	601.89	C-H out of plane

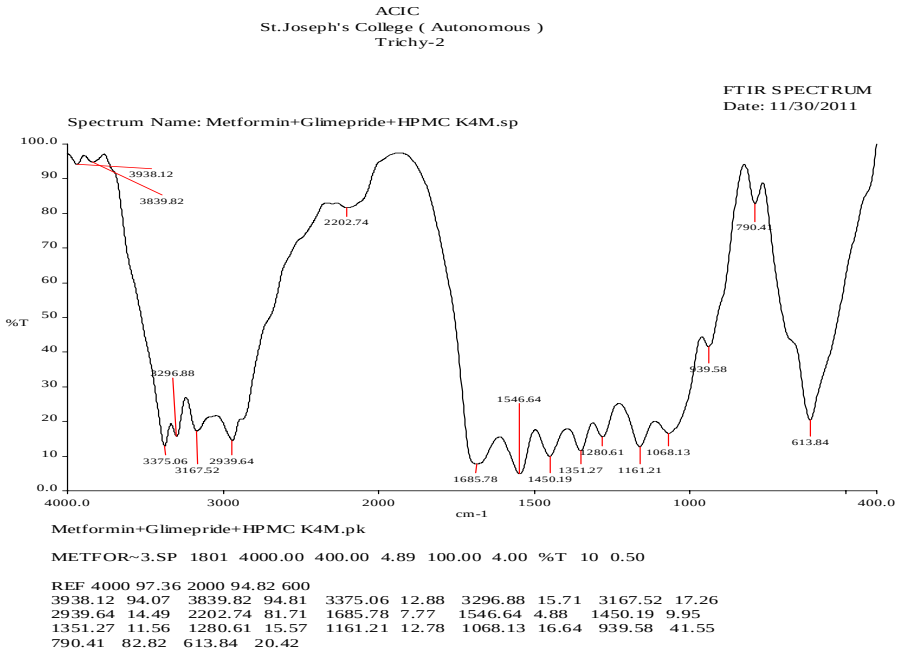


Fig : 13 IR Spectral assignment of physical mixture -I

Table No : 27

IR Spectral assignment of physical mixture –I

(Metformin HCl+Glimepiride+HPMCK4M)

S.No	Wave number (cm^{-1})	Assignment
1	3276.88	N-H stretching
2	3167.52	O-H stretching
3	2939.64	C-H stretching
4	1685.78	C=O stretching
5	1450.19	C=N stretching
6	1351.27	C=C stretching
7	931.12	C-H out plane bending

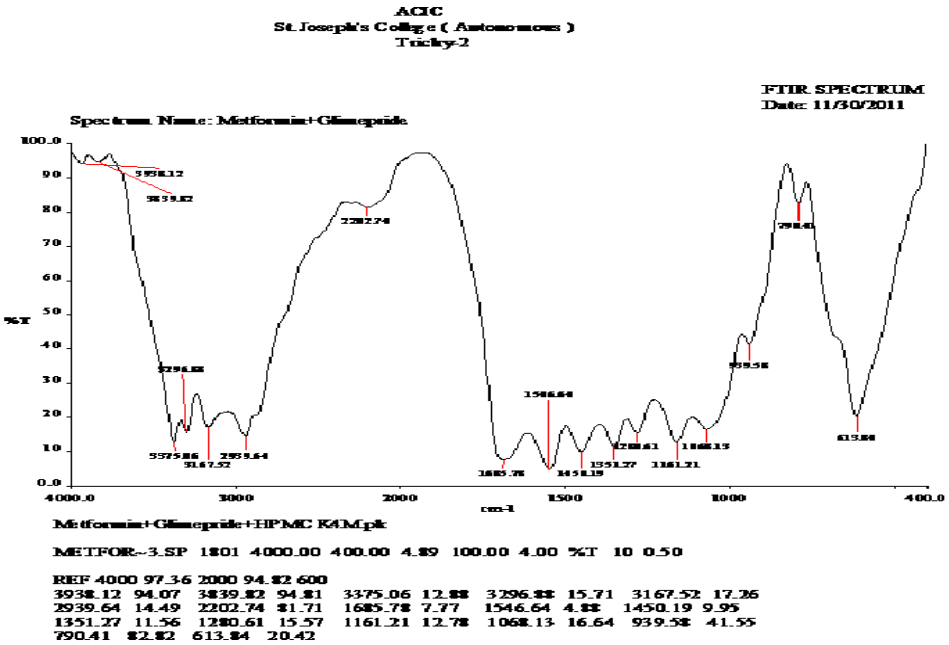


Fig : 14 IR Spectral assignment of physical mixture –II

Table No : 28

IR Spectral assignment of physical mixture –II

(Metformin HCl+Glimepiride+HPMCE-5)

S.No	Wavenumber (cm^{-1})	Assignment
1	3294.93	N-H stretching
2	3157.52	O-H stretching
3	2944.64	C-H stretching
4	1442.18	C=N stretching
5	1354.98	C=C stretching
6	1065.36	C-N bend
7	936.80	C-H out of plane

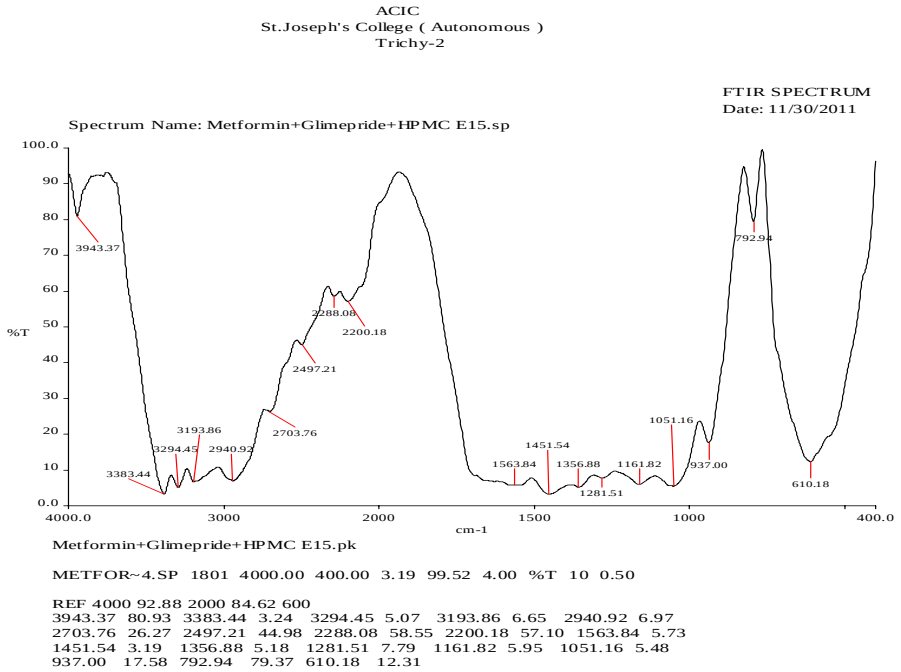


Fig : 15 IR Spectral assignment of physical mixture –III

Table No : 29

IR Spectral assignment of physical mixture –III

(Metformin HCl+Glimepiride+HPMCE-15)

S.No	Wavenumber (cm^{-1})	Assignment
1	3294.93	N-H stretching
2	3157.52	O-H stretching
3	2944.64	C-H stretching
4	1442.18	C=N stretching
5	1354.98	C=C stretching
6	1065.36	C-N bend
7	936.80	C-H out of plane

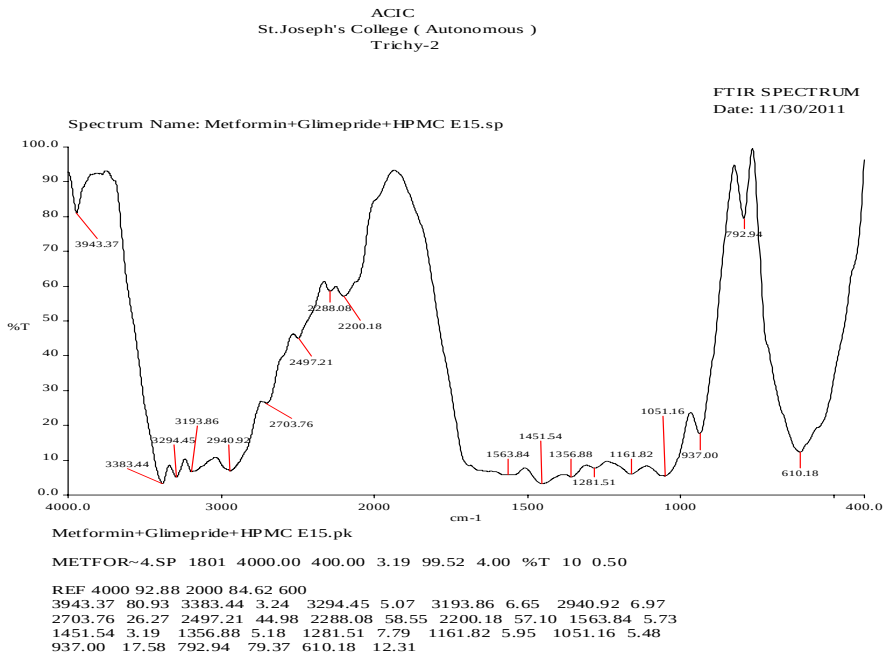


Fig : 16 IR Spectral assignment of physical mixture –IV

Table No : 30

IR Spectral assignment of physical mixture –IV

(Metformin HCl+Glimepiride+HPMCE-15)

S.No	Wavenumber (cm^{-1})	Assignment
1	3294.93	N-H stretching
2	3157.52	O-H stretching
3	2944.64	C-H stretching
4	1442.18	C=N stretching
5	1354.98	C=C stretching
6	1065.36	C-N bend
7	936.80	C-H out of plane

9.2 EVALUATION PARAMETER

9.2.1 Evaluation of granules of Floating Metformin HCl SR

The prepared granules were subjected to Pre-Compression parameters and the values are found to be within limits (Carr's index< 15% indicate excellent compressibility, Angle of repose<25° and Hausner's ratio<1.25 indicates good flow property). The results of granules were shown in the table no (31).

Table No : 31

Precompression parameters of Floating Metformin HCl SR

Formulation batch code	Angle of repose (°) ± S.D	Bulk density (gm) ± S.D	Tapped density (gm) ± S.D	Carr's Index (%) ± S.D	Hausner's Ratio ± S.D
M4	23.98±0.3	0.49±0.05	0.59±0.01	14.82±0.56	1.02±0.4
M8	24.34±0.2	0.54±0.03	0.61±0.03	13.92±0.67	1.04±0.3
M12	26.59±0.4	0.56±0.02	0.62±0.02	15.01±0.28	1.11±0.6

S.D = Standard Deviation, n=3

9.2.1.2 Physical Evaluation of Floating Metformin HCl SR tablet

All the formulated tablets of trial batch (M4,M8&M12) would lies within the Pharmacopoecial limits. The uniformity of weight lies between 0.640-0.690g, friability (0.3-0.5%), drug content (98.98-99.99%), hardness (4-6Kg/cm^2) and Floating lag time was found to be 29,28&25secs. The 29and 28secs of M4&M8 formulation indicates that the low viscosity grade polymer HPMCE-15 shows maximum floating lag time and 25secs of M12 indicates the high viscosity polymerHPMCK4M shows minimum floating lag time. The values are tabulated in the following table no(32).

Table No: 32

Physico – Chemical Characteristics of Floating Metformin HCl SR

Formulation batch code	Average weight of tablets(g) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%) ± S.D	Drug content (%) ± S.D	Floating lag time (Secs)	Total buoyancy time (Hrs)
M4	0.651 ±0.014	4.2±0.2	0.29±0.06	98.26±0.41	29±0.01	20
M8	0.649±0.022	4.8±0.1	0.3±0.04	98.99±0.52	28±0.23	20
M12	0.650±0.011	4.1±0.3	0.2±0.01	99.99±0.12	25±0.12	20

S.D = Standard Deviation, n=3

Table No:33

Determination of Swelling index for Floating Metformin HCl SR

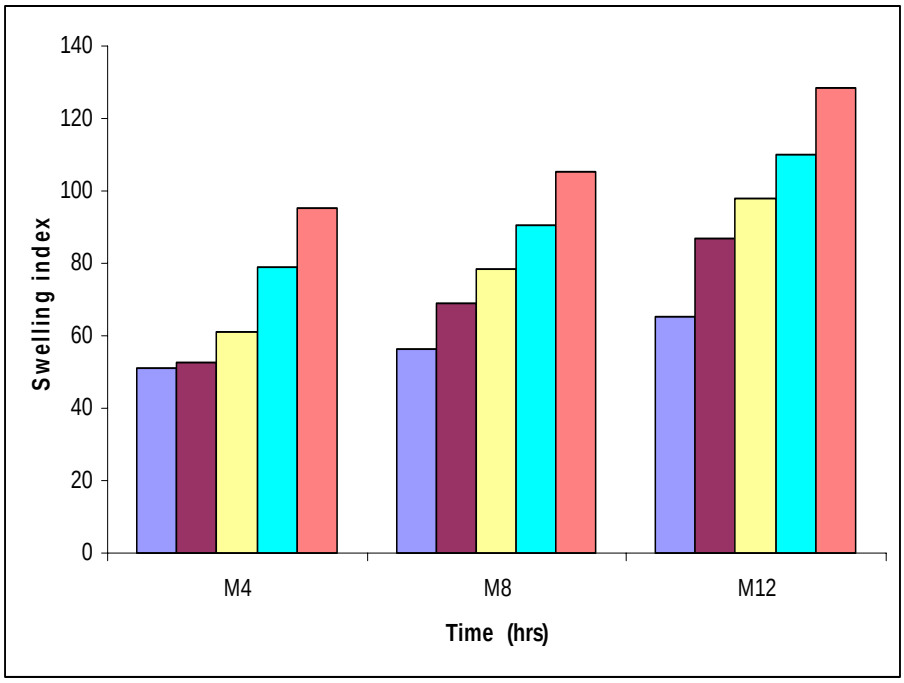
Time (hrs)	Formulation code		
	M4	M8	M12
1	50.83±0.5	56.55±0.2	65.50±0.26
2	52.44±0.4	68.74±0.7	86.75±0.75
3	61.12±0.1	78.56±0.6	97.82±0.28
4	79.03±0.3	90.52±0.5	109.89±0.9
5	95.23±0.26	105.23±0.3	128.55±0.5

The formulation M12 shows the higher swelling index this is due to the viscosity of the polymer had major effect on swelling process. From the above, it was clear that swelling of tablet with increase in time passes because the polymer gradually absorbed water due to hydrophilic in nature and swell, the water

absorption rate increases as the viscosity of the polymer increases. At the end, the polymer of the higher viscosity shows the maximum absorption. It was shown in above table no(33).

Fig : 17

Determination of Swelling index for Floating Metformin HCl SR



9.2.1.3 *In vitro* drug release profile

The *in vitro* drug release study was carried out by using USP dissolution apparatus II (paddle type) and results were tabulated in the table (34).

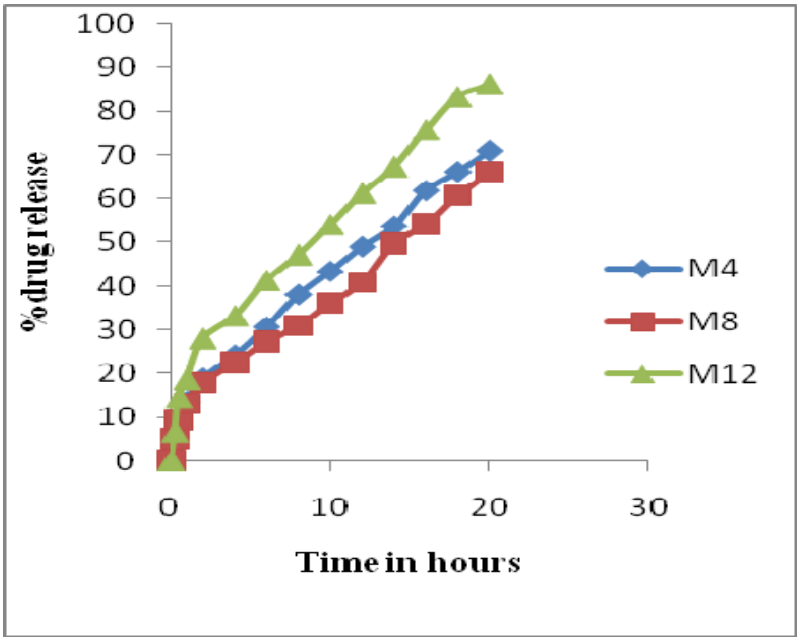
Table No: 34

***In vitro* drug release of Floating Metformin HCl SR**

Time (hrs)	Cumulative % of drug released (±S.D)		
	M4	**M8**	**M12**
0	0	0	0
0.25	4.31±0.31	5.07±0.73	6.59±0.52
0.5	9.66±0.60	9.15±0.12	14.55±0.58
1	13.54±0.54	13.01±0.14	18.59±0.54
2	18.85±0.86	17.82±0.86	27.96±0.94
4	24.15±0.12	22.46±0.42	33.11±0.19
6	30.57±0.56	27.28±0.29	41.24±0.26
8	37.99±0.98	31.03±0.34	47.13±0.14
10	43.31±0.31	36.17±0.13	53.98±0.96
12	48.92±0.99	40.98±0.92	61.18±0.12
14	53.68±0.67	49.69±0.63	67.24±0.24
16	61.79±0.75	54.33±0.34	75.67±0.64
18	66.09±0.96	60.78±0.76	83.24±0.23
20	70.8±0.82	66.19±0.18	**86.12±0.19**

Fig : 18

***In vitro* drug release profile of Floating Metformin HCl SR**



From the *in vitro* profile for Floating Metformin HCl SR (M4,M8&M12) the drug released was found to be 70.8%,66.19% & 86.12% respectively at the end of 20hrs. From this release profile, it was evident that the formulation M12 was suitable and it is suitable for SR formulation. (The formulation M4 &M8 did not follow the USP limit for SR i.e.,NLT 80%released at 20hrs)

9.2.2 Evaluation of Glimepiride immediate release tablet;

9.2.2.1Evaluation of granules

The results of precompression parameters for different formulation batches of Glimepiride immediate release tablet were shown in the table no(35).

Table no:35

Precompression Parameters of Glimepiride immediate release layer

Trial Batch G_1 to G_4

Formulation batch code	Angle of Repose (^{o}) ± S.D	Bulk Density (g/ml) ± S.D	Tapped Density (g/ml) ± S.D	Carr's Index (%) ± S.D	Hausner's Ratio ± S.D
G_1	29.71 ± 0.319	0.21 ± 0.01	0.23 ± 0.01	10.43 ± 0.31	1.09 ± 0.01
G_2	28.19 ± 0.101	0.19 ± 0.04	0.21 ± 0.03	9.91 ± 0.08	1.11 ± 0.01
G_3	29.48 ± 0.268	0.20 ± 0.02	0.22 ± 0.02	10.47 ± 0.29	1.11 ± 0.01
G_4	25.33 ± 0.136	0.21 ± 0.02	0.24 ± 0.01	9.66 ± 0.85	1.08 ± 0.02

S. D = Standard Deviation, n=3

The prepared granules were subjected to Pre-Compression parameters and the values are found to be within limits (Carr's index< 15% indicate excellent compressibility, Angle of repose<25° and Hausner's ratio<1.25 indicates good flow property). The results of granules were shown in the table no (35).

9.2.2.2Physical Evaluation of Glimepiride IR Tablets

The results of physico-chemical characterization of different formulation batches of Glimepiride IR tablet were summarized in the table no (36). The results shows that the formulation G1-G4 lies within IP limits weight variation, Hardness, Friability and Drug content.

Table no:36

Physico – Chemical Characteristics of Glimepiride immediate release layer Tablets

Trial Batch G_1 to G_4

Formulation batch code	Average weight of tablets(g) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%) ± S.D	Drug content (%) ± S.D
G_1	0.49 ± 0.006	5.2 ± 0.1	0.43 ± 0.01	99.15 ± 1.27
G_2	0.48 ± 0.004	5.7 ± 0.2	0.44 ± 0.05	98.07 ± 0.56
G_3	0.49 ± 0.009	5.1 ± 0.1	0.38 ± 0.03	99.26 ± 0.45
G_4	0.51 ± 0.006	5.5 ± 0.4	0.51 ± 0.03	99.97 ± 1.05

S. D = Standard Deviation, n=3

9.2.2.3In-Vitro Drug Release Profile

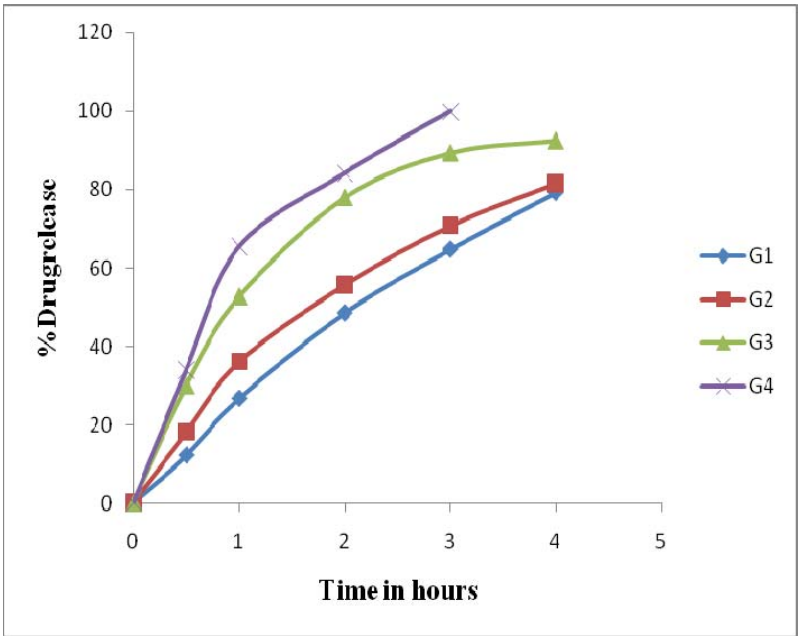
The *in vitro* drug release study was carried out by using USP dissolution apparatus II (paddle type) and results were tabulated in the table (37).

Table no : 37

Dissolution Profile of Formulation Trail Batch G_1 to G_4

Time(Hrs)	Formulation batch code			
	G1	G2	G3	G4
0	0	0	0	0
0.5	12.25±0.45	18.17±0.17	29.27±0,25	33.97±0.79
1	26.78±0.7	36.15±0.5	52.71±0.7	65.37±0.31
2	48.59±0.5	55.78±0.8	77.97±0.73	84.13±0.26
3	64.78±0.8	70.83±0.34	89.34±0.34	99.95±0.91
4	79.32±0.23	81.67±0.45	92.49±0.49	-

Fig : 19 *Invitro* Profile of Immediate release (G1-G4)



From the *in vitro* profile for formulation G1-G4 the drug released was found to be 64.78%, 70.83%, 89.34% & 99.95% at the end of 3 hrs. From the release profile G4 was suitable for IR formulation.

9.2.3 Evaluation of Floating Bilayer tablet of Metformin HCl SR & Glimepiride IR

The results of precompression parameters for different formulation batches of Floating Bilayer tablet of Metformin HCl SR & Glimepiride IR tablet were shown in the table no(35).

Table no: 38

Precompression Parameters of Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR

Formulation batch code	Angle of repose (°) ± S.D	Bulk density (gm) ± S.D	Tapped density (gm) ± S.D	Carr's Index (%) ± S.D	Hausner's Ratio ± S.D
C1	25.65±0.02	0.52±0.02	0.49±0.02	13.93±0.3	1.11±0.02
C2	26.93±0.3	0.54±0.04	0.54±0.34	14.92±0.5	1.19±0.1
C3	28.45±0.2	0.56±0.21	0.58±0.43	14.98±0.2	1.05±0.01
C4	24.78±0.08	0.51±0.31	0.52±0.02	12.93±0.02	1.12±0.03
C5	23.24±0.03	0.58±0.81	0.51±0.04	14.82±0.08	1.18±0.02
C6	23.67±0.34	0.49±0.09	0.59±0.03	15.92±0.72	1.12±0.2
C7	24.73±0.34	0.52±0.01	0.62±0.06	14.92±0.04	1.13±0.1
C8	23.94±0.02	0.56±0.2	0.68±0.34	13.92±0.05	1.16±0.4
C9	22.82±0.4	0.58±0.02	0.64±0.56	14.02±0.4	1.15±0.5

S.D = Standard Deviation, n=3

9.2.3.1 Physico – Chemical Characteristics of Floating Bilayer tablet of Metformin HCl SR & Glimepiride IR

The results of physico-chemical characterization of different formulation batches of Floating Bilayer tablet were summarized in the table no (39). The results shows that the formulation C1-C9 lies within IP limits weight variation, Hardness, Friability and Drug content.

Table no:39

Physico – Chemical Characteristics of Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR

Formulation batch code	Average weight of tablets(g) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%) ± S.D	Drug content (%) ± S.D	Floating lag time (Secs)	Total buoyancy time (Hrs)
C1	0.650±0.23	4.4±0.8	0.2±.02	97.98±0.25	25±0.2	19±.12
C2	0.649±0.22	4.8±0.6	0.3±0.04	98.99±0.52	26±0.23	20±0.34
C3	0.651±0.23	4.8±0.82	0.2±0.01	99.99±0.9	25±.18	20±0.24
C4	0.651 ±0.14	4.2±0.2	0.29±0.06	98.26±0.41	28±0.01	21±0.56
C5	0.654±0.23	5.32±0.3	0.3±0.01	96.99±0.6	27±0.85	20±0.9
C6	0.650±0.11	5.1±0.5	0.2±0.02	99.99±0.12	30±0.12	21±0.2
C7	0.654±0.42	5.2±0.12	0.26±0.03	97.67±0.23	32±0.45	21±0.1
C8	0.652±0.2	4.4±.12	0.24±0.01	98.23±0.45	29±0.38	22±0.8
C9	0.653±0.3	4.2±.9	0.04±0.12	97.34±0.56	30±0.64	24±.9

S.D = Standard Deviation, n=3

The floating lag time and total buoyancy time for formulation C3 was shown in the fig (20)

Fig : 20

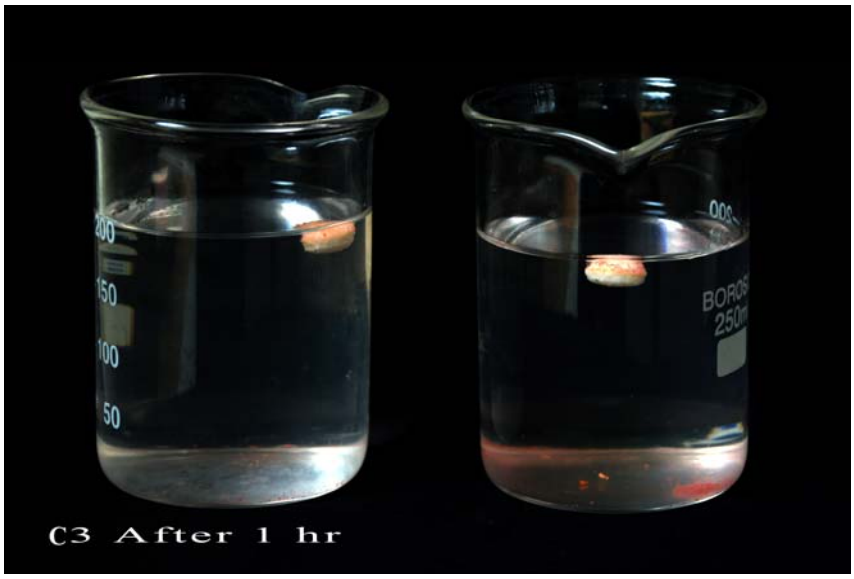
Floating Lag time of formulation C3

Fig : 20

Floating Lag time of formulation C3

Fig : 20

Floating Lag time of formulation C3



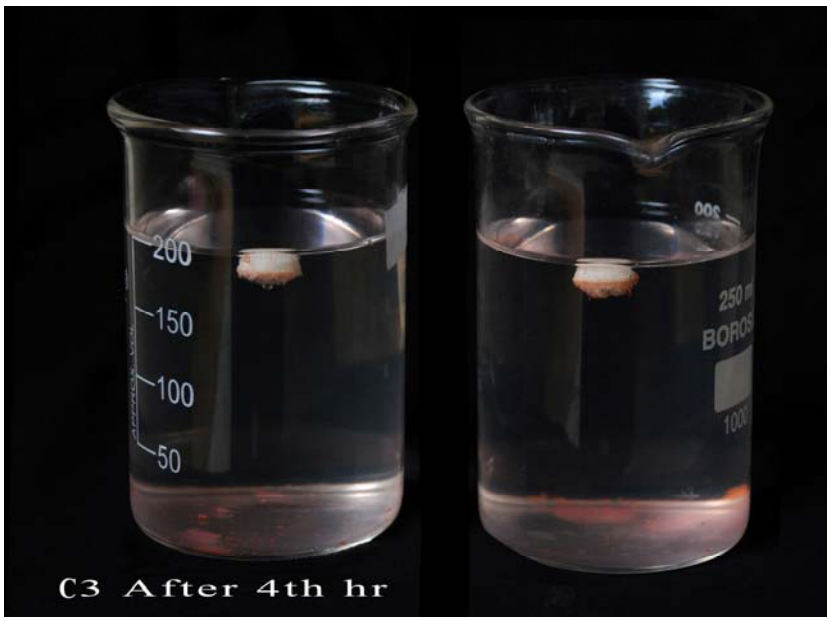


Fig : 20

Floating Lag time of formulation C3

Fig : 20

Floating Lag time of formulation C3

Table no: 40

Determination of Swelling index for Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR

Time (hrs)	Formulation code								
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
1	64.56±0.6	65.50±0.5	91.21±0.2	50.83±0.8	55.23±0.3	56.55±0.5	62.89±0.8	30.55±0.5	32.72±0.7
2	67.83±0.8	86.75±0.7	98.50±0.6	52.44±0.4	62.51±0.5	68.74±0.7	72.44±0.4	31.65±0.6	38.45±0.4
3	103.88±0.8	97.82±0.8	118.40±0.4	61.12±0.1	70.34±0.4	91.85±0.8	96.35±0.3	33.80±0.8	46.61±0.6
4	119.66±0.6	128.55±0.5	155.90±0.9	79.03±0.3	82.12±0.2	105.25±0.5	110.29±0.5	47.33±0.3	51.12±0.1
5	125.12±0.1	141.47±0.5	168.49±0.4	95.58±0.5	90.53±0.5	107.42±0.4	125.58±0.7	48.28±0.9	60.67±0.6

The swelling index of formulation C3,C6 &C7 shows the maximum of about 168.49,107.42 &125.58.From the results it was found that C3 formulation was found to have maximum swelling index due to combination of high viscosity polymers. It was shown in the fig. (21)

Fig: 21

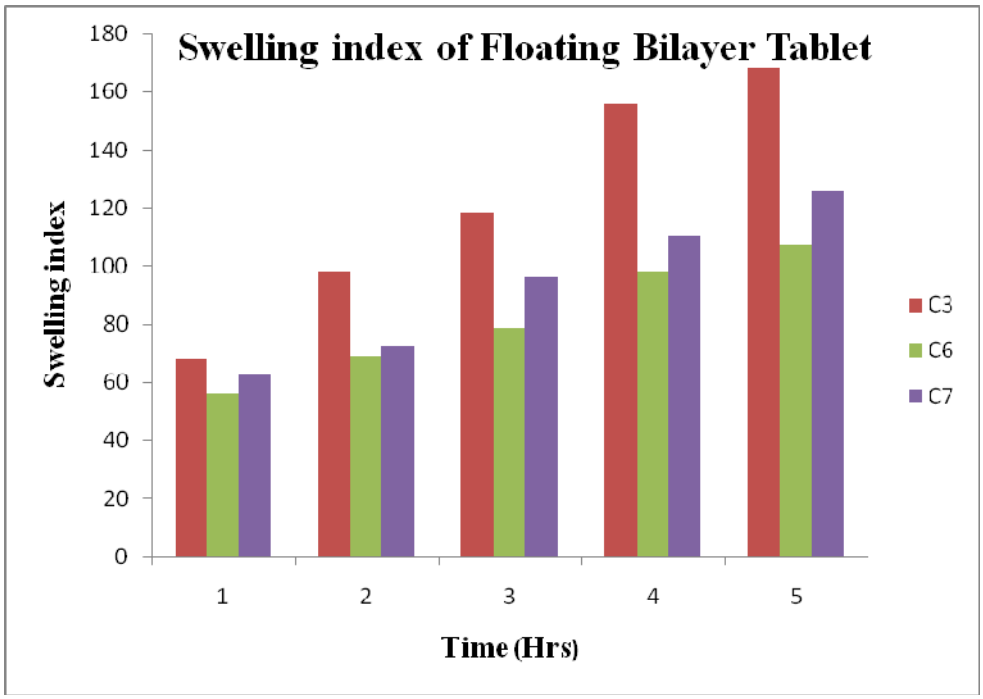
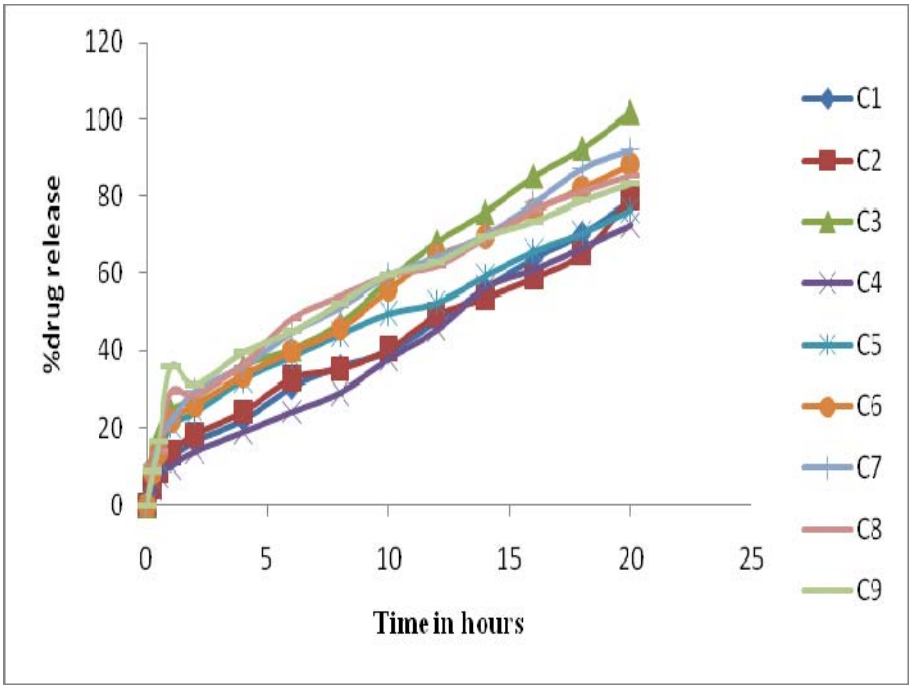

Swelling index of Floating Bilayer Tablet
Swelling index
180
160
140
120
100
80
60
40
20
0
1
2
3
4
5
Time (Hrs)
C3
C6
C7

Table no: 41

Dissolution study of Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR

Time in hours	Cumulative % of drug released (±S.D)								
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
0	0	0	0	0	0	0	0	0	0
0.25	4.9±0.21	5.25±0.54	10.35±0.2	4.52±0.23	6.65±0.23	8.99±0.45	10.58±0.3	9.69±0.1	8.76±0.9
0.5	8.18±0.5	9.27±0.2	18.19±0.8	7.99±0.3	11.64±0.5	13.66±0.4	16.44±0.6	14.11±0.3	16.55±0.4
1	11.93±0.8	13.67±0.4	24.69±0.9	10.07±0.7	20.54±0.5	21.99±0.9	21.78±0.7	19.24±0.9	24.82±0.3
2	16.47±0.4	18.34±0.3	27.95±0.9	13.86±0.8	24.15±0.1	26.07±0.7	29.71±0.7	26.87±0.8	29.32±0.3
4	22.17±0.1	24.42±0.2	36.25±0.2	19.02±0.1	3.7±0.7	33.78±0.7	36.04±0.4	32.71±0.1	35.04±0.4
6	30.69±0.6	32.92±0.9	40.52±0.5	24.28±0.2	38.58±0.5	39.96±0.9	44.81±0.8	39.67±0.6	39.73±0.7
8	35.89±0.8	35.27±0.2	47.24±0.2	29.32±0.3	44.4±0.4	45.87±0.8	51.43±0.4	48.59±0.5	45.11±0.1
10	39.74±0.7	40.52±0.5	58.34±0.3	37.98±0.9	49. 81±0.6	56.08±0.8	59.60±0.6	54.35±0.3	52.61±0.6
12	47.74±0.7	49.42±0.4	68.37±0.3	45.54±0.5	52.68±0.6	64.66±0.6	64.42±0.4	59.66±0.6	59.83±0.8
14	56.12±0.1	56.85±0.2	76.05±0.5	56.42±0.4	59.46±0.4	69.71±0.7	70.25±0.2	62.11±0.1	63.11±0.1
16	63.96±0.9	58.94±0.9	85.24±0.2	61.07±0.7	65.96±0.9	76.42±0.4	78.35±0.3	69.54±0.5	69.76±0.7
18	70.35±0.3	65.31±0.3	92.52±0.5	66.85±0.8	70.68±0.6	82.20±0.2	87.38±0.3	74.79±0.7	73.75±0.7
20	78.96±0.1	79.96±0.9	**101.92±0.1**	72.73±0.7	76.61±0.6	**88.47±0.4**	**92.25±0.2**	79.47±0.4	78.98±0.9

Fig : 22 *in vitro* release profile of floating bilayer tablet.



The formulation C3, C6&C9 the drug released was found to be 101.92%,88.47%&92.25% From the dissolution profile the formulation C1-C9 it was clearly shown that the formulation C3,C6 and C7 are suitable for SR formulation and it complies the USP limits.(NLT 80% released at 20hrs).

This is due to combination of low viscosity and high viscosity polymer. For C3 the percentage of polymer is 60&20% (HPMC K4M & HPMC E-15), C6 the percentage of polymer is 60&20% (HPMC E-15& HPMC E-5) and C7 the percentage of polymer is 20&60% (HPMC E-5& HPMC K4M).

From the formulation C3,C6 and C7 the formulation C3 was found to suitable for SR formulation, this is because the release of drug was retarded by employing the high viscosity polymer (HPMCK4M) when compared to low viscosity polymers HPMC E-15 and HPMC E-5.

Drug release kinetic models

Formulation (C3)

Fig : 23 Zero order plot

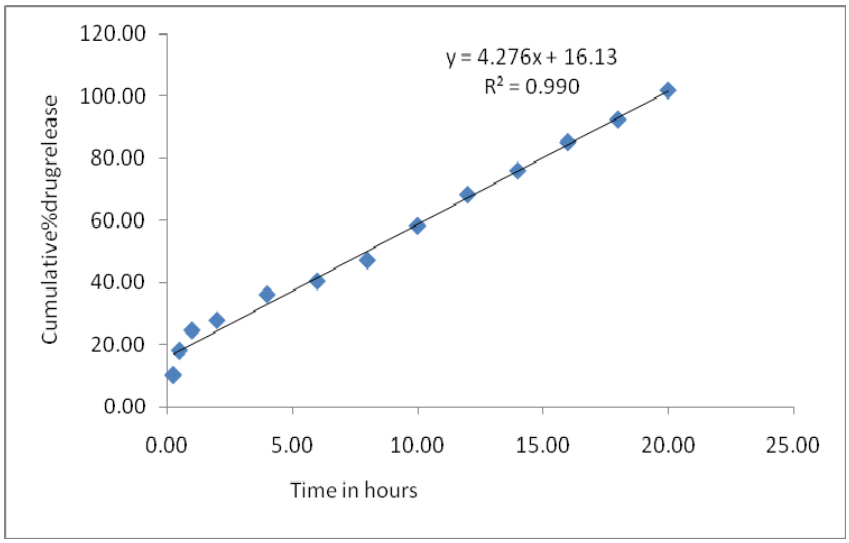


Fig : 24 First order plot

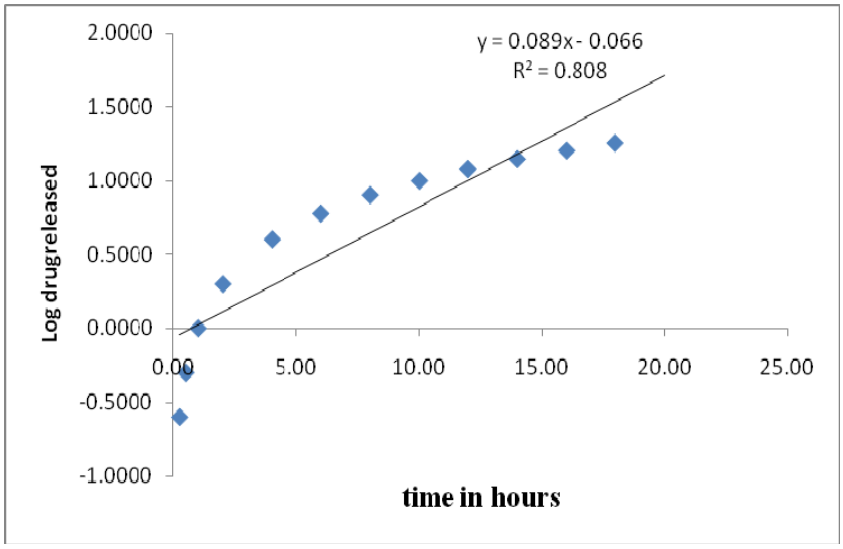


Fig : 25 Higuchi Model

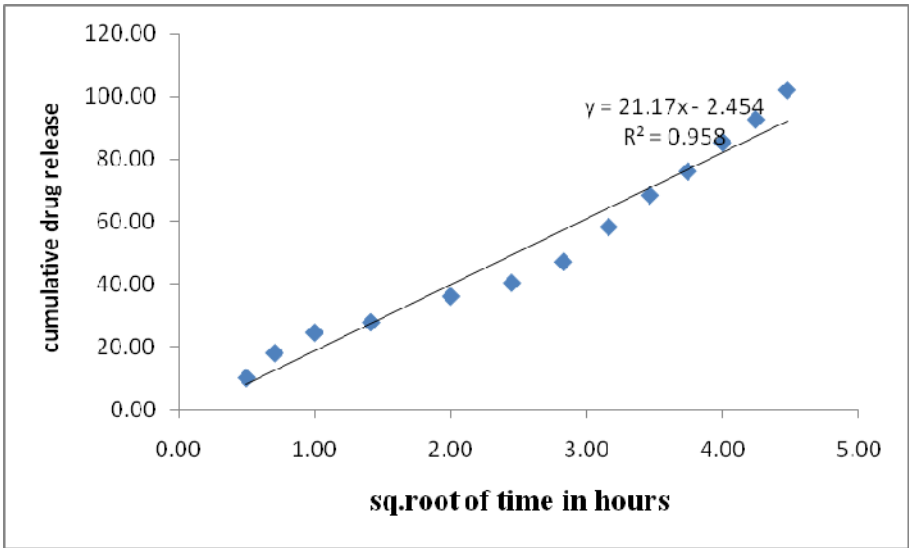
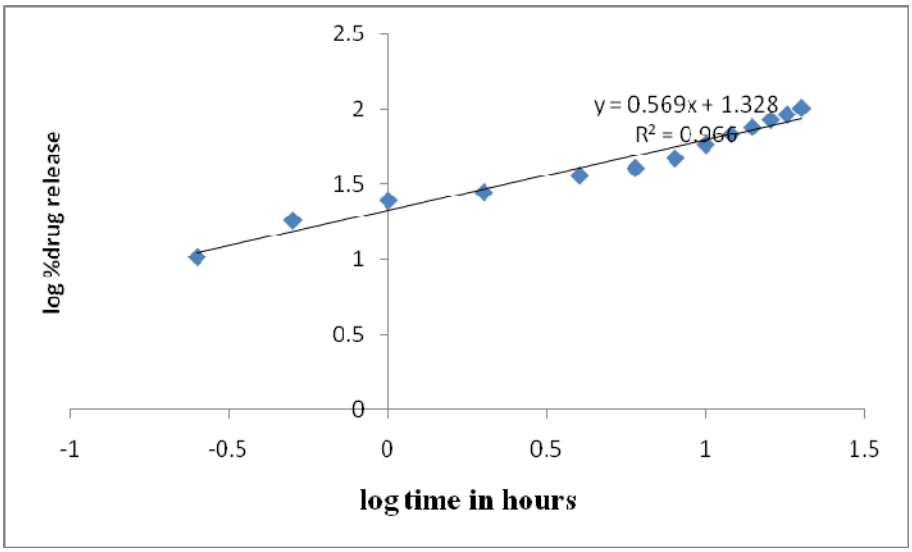


Fig : 26 Peppas Model



Drug release kinetic models

Formulation (C6)

Fig : 27 Zero order plot

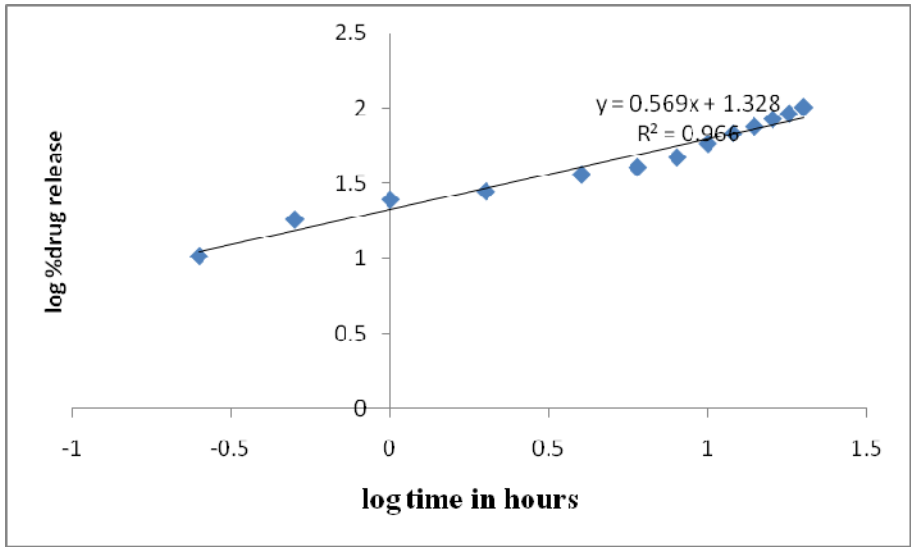


Fig : 28 First order plot

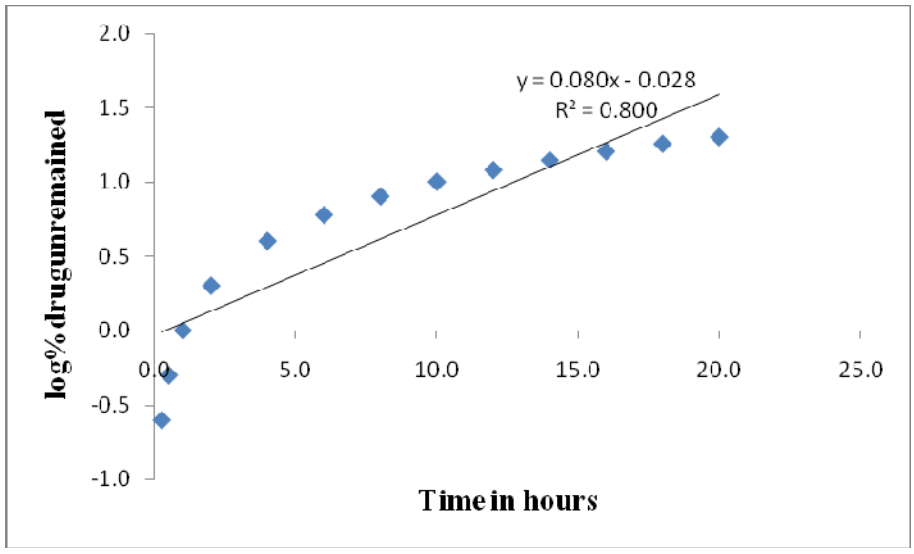


Fig : 29 Higuchi Model

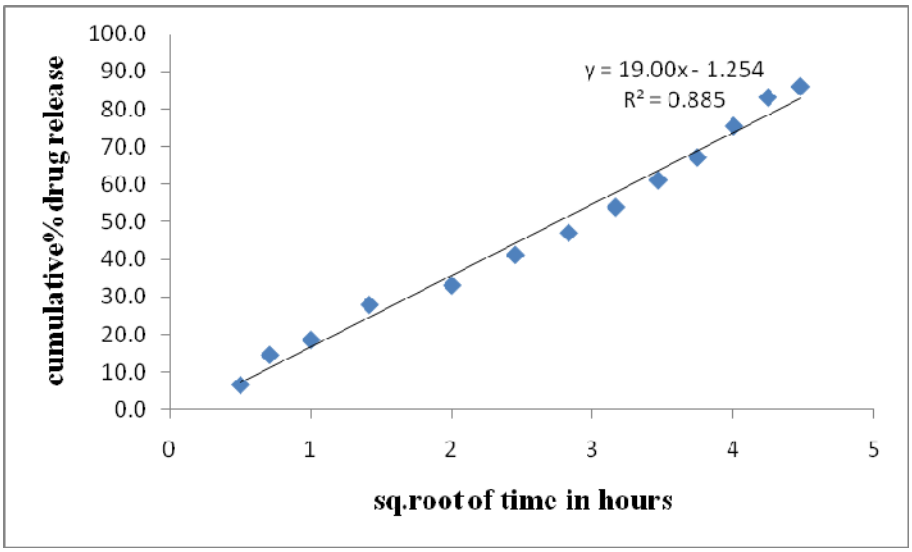
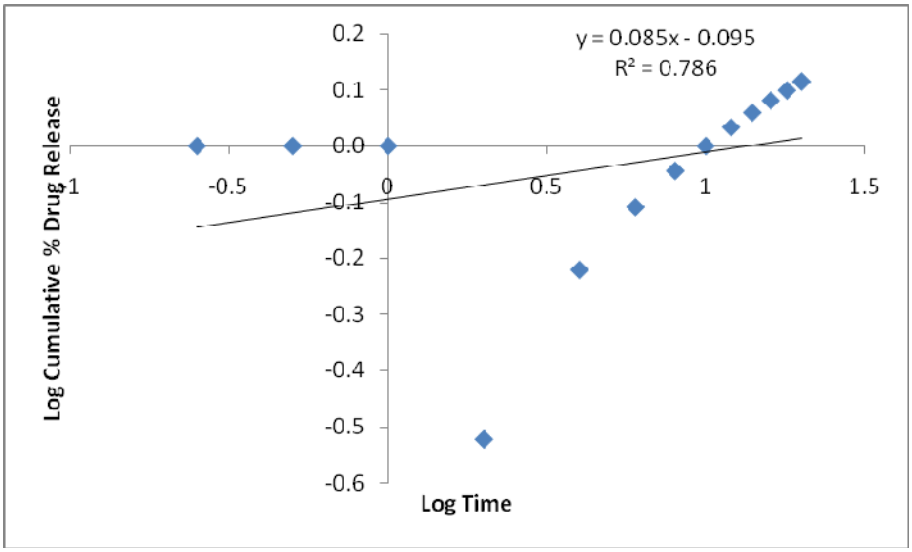


Fig : 30 Peppas Model



Drug release kinetic models

Formulation (C7)

Fig : 31 Zero order plot

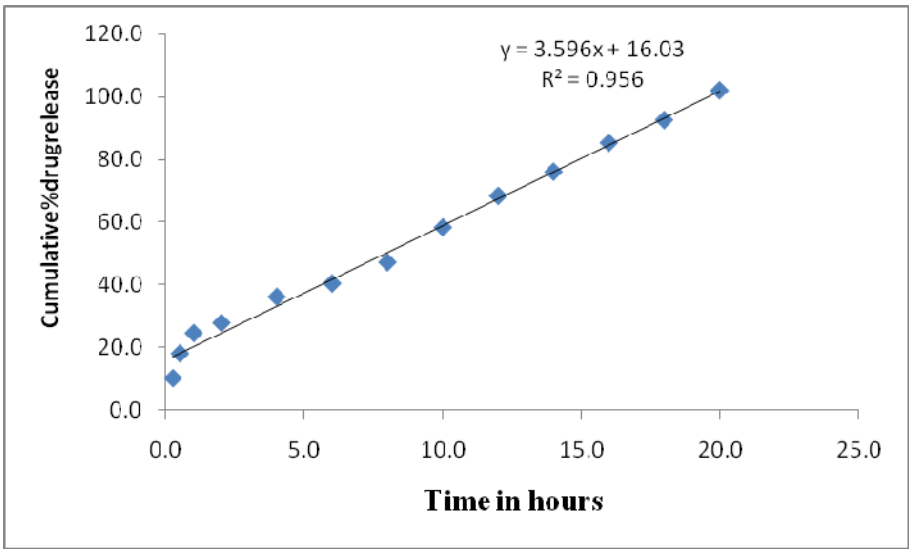


Fig : 32 First order plot

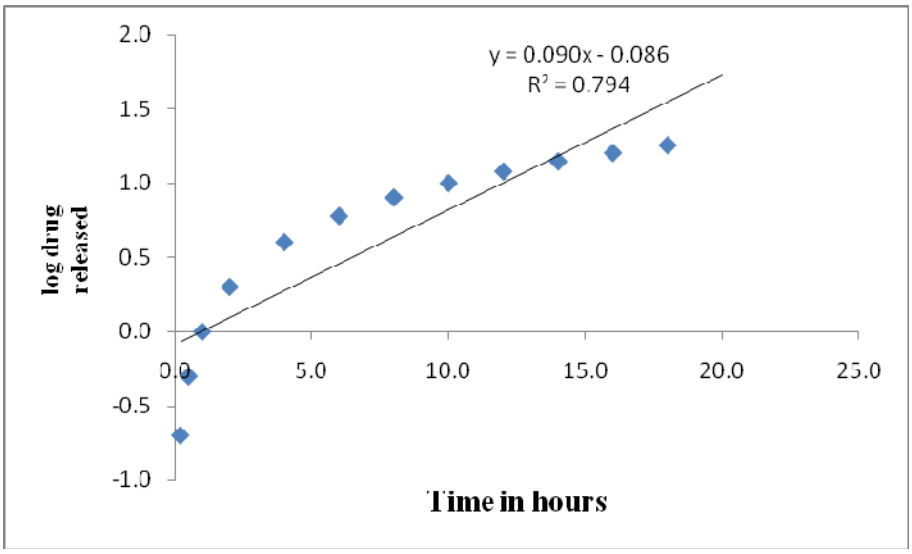


Fig : 33 Higuchi Model

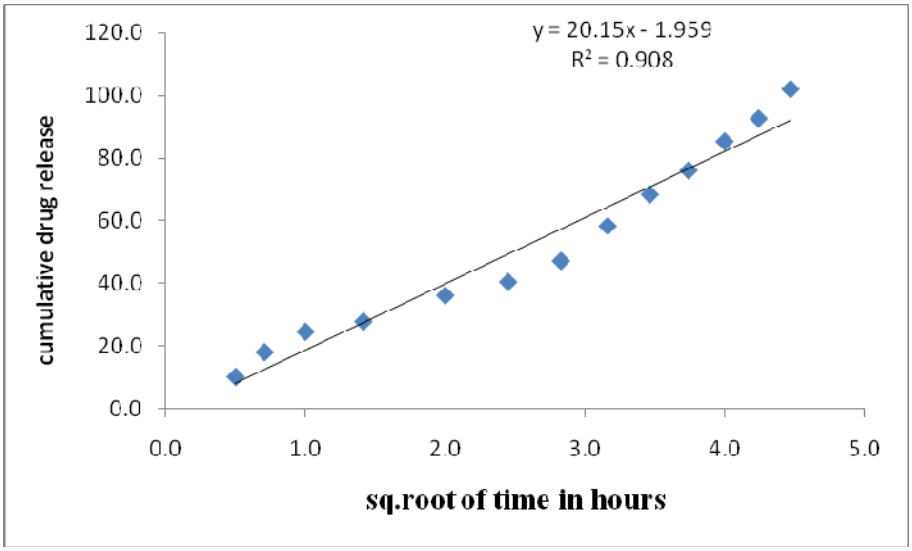


Fig : 34 Peppas Model

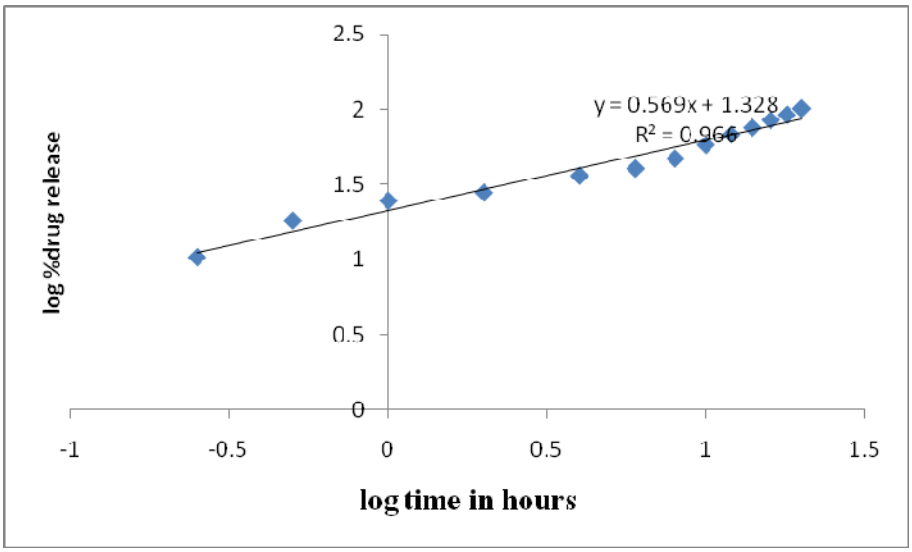


Table – 42

Descriptive Statistics of Regression and Parameters of the Mathematical Models for the Dissolution Data of floating Bilayer tablet of Metformin HCl SR & Glimepiride IR

Kinetic models	Statistical parameter	C3	C6	C7
Zero-Order	R^2	0.990	0.879	0.956
	m	4.276	3.765	3.956
	K	16.13	15.06	16.08
First-Order	R^2	0.794	0.801	0.794
	m	0.090	0.080	0.09
	K	-0.086	-0.028	-0.081
Higuchi	R^2	0.958	0.885	0.908
	m	21.17	19.0	20.10
	K	-2.454	-1.125	-1.998
Peppas	R^2	0.966	0.786	0.932
	n	0.596	0.08	0.43
	K	1.328	-0.094	0.9

The results of dissolution data of optimized floating bilayer tablet of Metformin HCl SR and Glimepiride IR formulation C3,C6 &C7were fitted to various drug release kinetic models i.e., Zero-Order, First Order, Higuchi and Peppas models to find out the relese mechanism of the drug.

The calculated R^2 and K values are shown in the table no(42). From the results it was concluded that all formulation follows zero-order than first order. It is acceptable for sustained release formulation to fit in zero-order than in first-order.

From Peppas model, n value was used to describe the release mechanism of drug from sustained release dosage form. The diffusion co-efficient of 'n' value of peppas model 0.5-1 indicates the release of drug follows anamalous transport of Non-fickian diffusion. (corresponds to diffusion and erosion mechanism or mixed order kinetics) C3 formulation diffusion co-efficient 'n' value of peppas model 0.596 it follows within the limits.

Stability study

The physico-chemical and *in vitro* release of floating Bilayer tablet kept at 40ºC/75% RH were studied for 3 months as per ICH guidelines. The parameters are shown in the table (43).

Table - 43

Stability study for Floating Bilayer tablet (C3)

S.No	Parameters	Initial	After 3 months	Acceptance criteria
1	Description	Complies	Complies	White color SR layer and pink color IR layer
2	Average weight (mg)	649.8	648.9	640-660
3	Friability (%)	0.2	0.19	Less than 1
4	Hardness (Kg/cm^2)	4.5	4.2	4-6
5	Drug content (%)			
	Metformin HCl	99.96	99.03	95%-105%
	Glimepiride	98.76	97.9	90%-110%
6	Floating lag time (secs)	25	24	25
7	Total buoyancy time (hrs)	20	20	20

From the description, average weight, friability, hardness, drug content, floating lag time and total buoyancy time studies carried out after 3 months completion it was clear that the formulation C3 revealed no significant change from initial values which indicates the formulation was stable.

***In vitro* dissolution test**

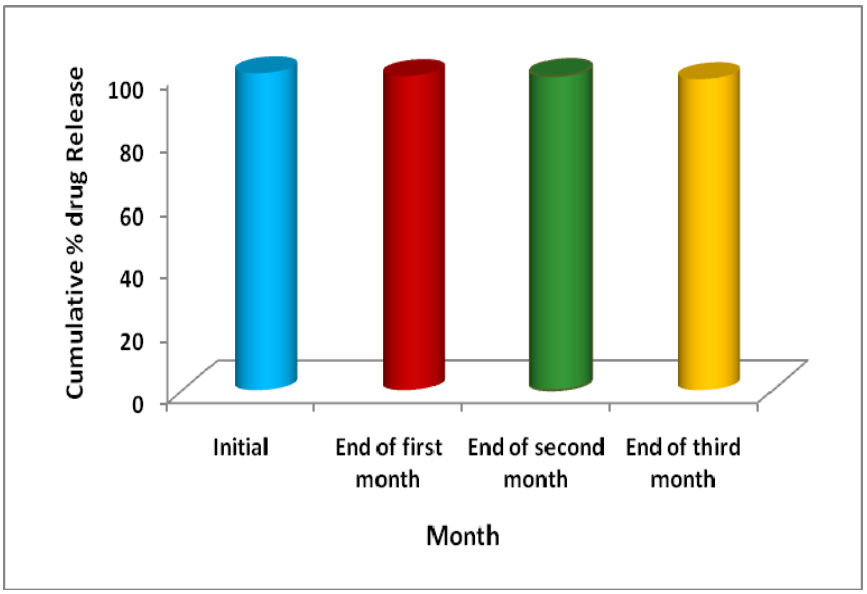
The physical, chemical and *In vitro* release of floating Bilayer tablet of Metformin HCl & Glimepiride tablets kept at 40ºC/75% RH were studied for 3 months as per ICH guidelines. The *in vitro* release study was carried out by using USP dissolution apparatus II and results are shown in table (44).

Table - 44

Comparative *In vitro* Dissolution profile of floating Bilayer tablet of Metformin HCl & Glimepiride (C3). Before and after storage at 40ºC/75% RH

Time in hours	Cumulative % of drug released (±S.D)			
	Initial	End of first month	End of second month	End of third month
0	0	0	0	0
0.25	10.5±0.2	10.5±0.2	10.35±0.2	9.95±0.2
0.5	18.06±0.8	17.19±0.8	18.19±0.8	17.19±0.8
1	23.69±0.9	24.69±0.9	24.69±0.9	23.69±0.9
2	29.95±0.9	27.95±0.9	27.95±0.9	28.95±0.9
4	35.25±0.2	36.25±0.2	36.25±0.2	35.25±0.2
6	41.52±0.5	40.52±0.5	40.52±0.5	42.52±0.5
8	48.24±0.2	47.24±0.2	47.24±0.2	48.24±0.2
10	59.34±0.3	58.34±0.3	58.34±0.3	57.34±0.3
12	68.37±0.3	68.37±0.3	68.37±0.3	69.37±0.3
14	76.05±0.5	76.05±0.5	76.05±0.5	75.05±0.5
16	89.24±0.2	85.24±0.2	85.24±0.2	88.24±0.2
18	92.52±0.5	92.52±0.5	92.52±0.5	92.52±0.5
20	**100.92±0.1**	**100.02±0.5**	**99.99±0.2**	**98.86±0.3**

Fig : 35 Stability study of formulation C3 at the end of 3 months



From the dissolution profile, the formulation C3 was selected for the stability studies. The cumulative % of drug release at zero month was 100.92% at 20hrs. After first and third month completion the cumulative % of drug release was 100.02%,99.99% &98.86 at the end of 20hrs. The formulation C3 revealed that no significant change from initial values which indicates the formulation were stable.

SUMMARY AND CONCLUSION

Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR were formulated using HPMC K4M, HPMC E-15 and HPMC E-15 in alone (80%) and in combination of different percentage of polymer (20&60%,40&40% and 60&20%).

Three different formulations (M4, M8 &M12) of floating Metformin HCl SR tablets are prepared by employing the hydrophilic polymer HPMC in different viscosity grades in the percentage of 80%. From that M12 formulation were found to be suitable for formulating SR tablet by its *in vitro* release. From the M12 formulation, it was clear that when the polymer concentration increases it decreases the release rate.

Formulations of C1-C9 of floating Bilayer tablets are prepared by combining the different viscosity polymers (HPMC K4M+HPMC E-15, HPMC E-15+HPMC E-5 & HPMC E-5+HPMC K4M) in the percentage 0f 20&60%,40&40% and 60&20%

The formulation C3 (HPMC K4M[60%]+HPMC E-15[20%]), C6 (HPMCE-5 [20%]+HPMCE-15[60%]) and C7 (HPMC K4M[60%] + HPMC E-5[20%]) were found to suitable for formulating SR by its *in vitro* release studies and it show release about 101.92%, 88.47% and 92.25%.

From the C3 formulation it was shown that the percentage of high viscosity polymer can be reduced by adding low viscosity polymer.

From the dissolution profile of formulation C3 it was well understood that the release of drug from its formulation can be improved by combining the low and high viscosity polymers compared to formulating M12 high viscosity polymer alone. From this study it was concluded that Floating time increases, it decreases the release rate. So it suitable for sustained release formulation.

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